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(54) Title: EXTENDED cDNAs FOR SECRETED PROTEINS

(57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed
along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.
Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mischaeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

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portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported 10 sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- α , interferon- β , interferon- γ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

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also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., 10 Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream 15 regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include 20 sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5' coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted 25 proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10⁴-10⁶ fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

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Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the 20 cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

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The present invention also relates to secretion vectors capable of directing the secretion of a protein of

interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEO ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

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Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the 30 preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

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Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and NotI. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

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Figure 10 is an alignment of the protein of SEQ ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516).

Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseg accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID-NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex 10 (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

Detailed Description of the Preferred Embodiment

15 I. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

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may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

EXAMPLE 1

Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1 μg of RNA was incubated in a final reaction medium of 10 μl in the presence of 5 U of T₄ phage RNA ligase in the buffer provided by the manufacturer (Gibco · BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 μl of ³²pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH₄, NaBH₃CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

EXAMPLE 2

Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step.

Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

+Cap:

25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)

·Cap:

5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

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include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

EXAMPLE 3

Coupling of the Dialdehyde with Biotin

5 The oxidation product obtained in Example 2 was dissolved in 50 μl of sodium acetate at a pH of between 5 and 5.2 and 50 μl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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EXAMPLE 4

Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.

Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.

Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure.

For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment.

Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

EXAMPLE 5

Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

EXAMPLE 6

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Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with ³²pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing 30 conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced,

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

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In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

EXAMPLE 7

Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula H₂N(R1)NH₂ at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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EXAMPLE 8

Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100μ of 0.1N sodium hydroxide, 1.5μ g mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

EXAMPLE 9

Oxidation of Diols

Up to 1 OD unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

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Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

EXAMPLE 10

Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

EXAMPLE 11

Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO₄/accetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO₄/accetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The

derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

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10 μ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39 μ l of 10 mM urea and 2 μ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45 μ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added, 100 µl

fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with 32P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with ³²P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

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GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)
GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID NO:6)

dehydrogenase

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3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.
 - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the 20 presence of cDNA.
 - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
 - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.
 - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEQ ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

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oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

EXAMPLE 12

Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA + RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this 10 procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first 15 and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards, supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold 20 Spring Harbor Laboratory Press, 1989.

II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

EXAMPLE 13

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Preparation of mRNA

Total human RNAs or PolyA + RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by 30 two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe complementary to the oligonucleotide tag.

EXAMPLE 14

cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

20 Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

EXAMPLE 15

Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

EXAMPLE 16

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporaved into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

EXAMPLE 17

Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

15 MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL),

BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and
peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc.

Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn
helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

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Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

EXAMPLE 18

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Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the 10 sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNA. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the 15 sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to 20 the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be 30 identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

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the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

EXAMPLE 19

Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE TM database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

EXAMPLE 20

Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit α and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the 30 corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA

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sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

EXAMPLE 21

Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENE™ was screened to identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

EXAMPLE 22

Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

Approximately half of the CDNA sequences in NETGENETM contained such as ORF. The ORF of the CDNA sequences in NETGENETM contained such as ORF.

Approximately half of the cDNA sequences in NETGENETM contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

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EXAMPLE 23

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using
the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequencereporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After
introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be
harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the
medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which
encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAGTM database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAGTM database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAGTM database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAGTM database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, 20 as described below in Example 25.

EXAMPLE 25

Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

EXAMPLE 26

Evaluation of Expression Levels and Patterns of mRNAs

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Corresponding to 5' ESTs or Extended cDNAs

Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internalrestriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More 15 preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

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For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; *Proc. Natl. Acad. Sci. U.S.A.* 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are 30 obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides.

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After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density

nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al.

(Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., supra) or synthesized and then addressed to the chip (Sosnowski et al., supra). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are
synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

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The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino acids of the sequences of SEQ ID NOs: 40-140 and

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242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

EXAMPLE 27

General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENETM database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

1. Obtaining Extended cDNAs

10 a) First strand synthesis

The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

b) Second strand synthesis

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A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outerprimer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

5 2. Seguencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is closed in an appropriate vector such as pED6dpc2, as described in section 3.

b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose

30 primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

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walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the 5 length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls 10 and validation steps are carried out as described in example 15.

3. Cloning of Full Length Extended cDNAs

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The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, 30 contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

4. Computer Analysis of Full Length Extended cDNA

Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S=72; identity=70%; and length = 40 nucleotides.

Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not

of interest are searched as follows. a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was

15 carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer

RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN

programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having
more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 90%, were flagged.

b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it.

The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

c) Identification of functional features

Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

d) Homology to either nucleotidic or proteic sequences

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Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

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have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs

are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001.

Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

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alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

b) Manual sequence selection

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Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

EXAMPLE 28

Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

.39.

The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or

functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the
members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in
the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at
http://expasy.hcuge.ch/sprot/prosite.html. Prosite_convert and prosite_scan programs
(http://ulrec3.unil.ch/ftpserveur/prosite scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

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proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite_scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences

encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) Preferably, the probe is designed to have a T_m of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

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The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X10⁶ dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X10⁶ dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

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EXAMPLE 29

Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where
the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is
contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended
cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200
nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as
oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in
6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide
containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

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with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

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The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na + concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

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stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

30 EXAMPLE 30

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Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

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It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEO ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID Nos. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID Nos. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

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The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with Pstl, blunt ended with an exonuclease, digested with Bglll, purified and ligated to pXT1, now containing a poly A signal and digested with Bglll.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

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Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques.

In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

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the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

(Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro ExpressTM Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

EXAMPLE 31

20 <u>Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface</u>

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various

amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the
cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an
unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein
bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled
protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in
Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

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The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is

10 beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 33

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Activity as Immune System Regulators

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The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988;

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol, 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

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Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation
of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins ercoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

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myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways.

Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent.

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Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte

antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will

be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example,

blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue

transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune

reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7

lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7
activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen

(e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural

ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte

antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an

immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing

tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the

necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance

in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

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of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

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Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

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The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β₂ macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 34

Assaying the Proteins Expressed from Extended cDNAs

or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

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pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 35

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

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nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and 5 other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair 10 processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

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Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as

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Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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EXAMPLE 36

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

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activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36A

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Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

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Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

EXAMPLE 37

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Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as,for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 38

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

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molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

EXAMPLE 38A

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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EXAMPLE 38B

Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 39

Identification of Proteins which Interact with

Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof

are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes.

30 The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase. 5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

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Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

EXAMPLE 40

Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 µM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 41

Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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EXAMPLE 42

Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

EXAMPLE 43

Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

EXAMPLE 44

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Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

EXAMPLE 45

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Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

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nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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EXAMPLE 46

Dot Blot Identification Procedure

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P32 using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

EXAMPLE 47

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Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P³². The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

EXAMPLE 48

Identification of Tissue Types or Cell Species by Means of

Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semi-qualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that
reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example ¹²⁵I, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such 25 labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

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The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

30 carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

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in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 μ l, and containing from about 1 to 100 μ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

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The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 49

Radiation hybrid mapping of Extended cDNAs to the human genome

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Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique 5 is described by Benham et al. (Genomics 4:509-517, 1989) and Cox et al., (Science 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., Science 274:540-546, 10 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr.iidine kinase (TK) (Foster et al., Genomics 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., Eur. J. Hum. Genet. 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., Genomics 29:170-178, 1995), the 15 region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., Genomics 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., Genomics 11:701-708, 1991).

EXAMPLE 50

Mapping of Extended cDNAs to Human Chromosomes using PCR techniques

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Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see 25 Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 μ Cu of a 32 P-labeled deoxycytidine triphosphate. The PCR is 30 performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

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PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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EXAMPLE 51

Mapping of Extended 5' ESTs to Chromosomes

Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 μM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 μg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research

Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 μ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

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70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl₂) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of
biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., supra.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given
chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

EXAMPLE 52

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Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms 30 chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 53

Identification of genes associated with hereditary diseases or drug response

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

EXAMPLE 54

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Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the

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extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

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Use of Extended cDNAs or 5' ESTs to Clone Upstream

Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the 5 GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or 'EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 μ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 μ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc), and 1 μ l of the Tth polymerase 50X mix in a total volume of 50 μ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 μ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 μ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalkerTM kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

5 In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

EXAMPLE 56

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, p\u00edgal-Basic, p\u00edgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, B galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

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Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 57

Cloning and Identification of Promoters

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Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

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Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

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Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

EXAMPLE 58

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Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

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EXAMPLE 59

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an 10 intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from 15 that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be 20 synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these moleucles, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense 30 oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO
92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control
recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain
"hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop"

10 structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

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Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10⁻¹⁰M to 1x10⁻⁴M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10⁻⁷ translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

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It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., *supra*.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the

effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to
antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

EXAMPLE 60

Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as

Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target
gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based
upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived
with known gene sequences that have been associated with a particular function. The cell functions can also be

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predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

EXAMPLE 61

Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

EXAMPLE 62

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<u>Use Of Signal Peptides Encoded By 5' Ests Or Sequences</u> <u>Obtained Therefrom To Import Proteins Into Cells</u>

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 63

Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

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EXAMPLE 64

Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 30) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

15 A) Proteins which are closely related to known proteins

Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

25 Proteins of SEQ ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs: 175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

5 Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 : 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

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alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8: 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi et al, FEBS Lett., 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink et al., Hum. Mol. Gent., 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEO ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

Proteins of SEQ ID NOs: 149, 150 and 211

The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle *et al, J. Biol. Chem.*, 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response.

Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably

of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AF019225). The matched protein is a secreted high density lipoprotein associated with apoA-I-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

Protein of SEQ ID NO: 163

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The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

C) Proteins homologous to a domain of a protein with known function

Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369: 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

Protein of SEQ ID NO: 153

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The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction
and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

Protein of SEQ ED NO: 240

The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

Protein of SEO ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in *Saccharomyces cerevisiae*. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEQ ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

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types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

Protein of SEQ ED NO: 167

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The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEQ ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

Protein of SEO ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily.

The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

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Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

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As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other 25 protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing 30 such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

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SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

TABLE I

SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	82
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	81
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	53
51	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
52	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
53	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
54	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
56	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
57	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
60	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
61	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
62	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	69
63	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	49
64	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
65	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	53
66	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	57
67	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	54
68	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	55
69	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	58
70	U.S. Provisional Patent Application Serial No. 60/095,116, filed Aug. 10, 1998	59

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12	CONT. TABLET		**
1.0. 1.0.	71	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	60
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81 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 65 82 U.S. Provisional Patent Application Serial No. 60/096,957, filed Dec. 17, 1997 54 83 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 78 84 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 63 85 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 65 86 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 152 87 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 66 88 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 67 89 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 67 90 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 68 91 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 68 91 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 98 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 97 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176	79	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	61
82 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 54	80	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	130
83 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 78 84 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 63 85 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 65 86 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 152 87 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 66 88 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 67 89 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 60 90 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 68 91 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 98 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 99 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	81	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	65
84 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 63 85 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 65 86 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 152 87 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 66 88 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 67 89 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 60 90 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 61 91 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 62 92 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 170 95 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 170 96 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 170 97 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 170 98 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 176 102 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 187	82	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	54
85 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 65 86 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 152 87 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 66 88 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 67 89 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 60 90 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 91 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 98 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 99 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	83	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	78
86	84	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	63
87 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 66 88 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 67 89 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 60 90 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 91 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 98 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 63 101 U.S. Provisional Patent Application Serial No. 60/096,957, filed Dec. 17, 1997 187	85	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	65
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89 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 60 90 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 68 91 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 101 U.S. Provisional Patent Application Serial No. 60/096,957, filed Dec. 17, 1997 187 102 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 103 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 104 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 105 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 105 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 105 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 106 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 107 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187 107 U.S. Provisional Patent Application Serial No. 60/069,957, fil	87	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	66
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91 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 61 92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 70 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/096,116, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/096,157, filed Dec. 17, 1997 187	89	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	60
92 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 62 93 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 166 94 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 70 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 100 U.S. Provisional Patent Application Serial No. 60/099,957, filed Dec. 17, 1997 187	90	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	68
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94 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 70 95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/099,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	92	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	62
95 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 73 96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	93	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	166
96 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 63 97 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	94	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	70
97 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 52 98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/099,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	95	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	73
98 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 62 99 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	96	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	63
99 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 176 100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	97	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	52
100 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998, 63 101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	98	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	62
101 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 187	99	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	176
	100	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	63
U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	101	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	187
	102	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	190
103 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 83	103	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	
104 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 180	104		
105 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998 64	105		
106 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 69	106		

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109 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 43	107	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	40
110 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 82	108	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	77
110 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 76	109	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	43
112 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 46 113 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 46 114 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 47 115 U.S. Provisional Patent Application Serial No. 60/066,677, filed Nov. 13, 1997 53 116 U.S. Provisional Patent Application Serial No. 60/066,677, filed Nov. 13, 1997 53 117 U.S. Provisional Patent Application Serial No. 60/068,677, filed Apr. 13, 1998 74 118 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 71 119 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 145 120 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 58 121 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 58 122 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 40 123 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 40 125 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 44 126 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 45 127 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 45 128 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 47 129 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 55 130 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 56 131 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 57 132 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 57 133 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 57 134 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 57 135 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 57 136 U.S. Provisional Patent Application Serial	110	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	1
113 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 45	111	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	76
114 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 47	112	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	43
115 U.S. Provisional Patent Application Serial No. 60/056,677, filed Nov. 13, 1997 53	113	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	46
116	114	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	47
1177 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 74	115	U.S. Provisional Patent Application Serial No. 60/066,677, filed Nov. 13, 1997	53
118 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 71	116	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	58
119 U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 145	117	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	74
120 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 67	118	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	71
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287	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	120
288	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	121
289	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	122
290	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	123
291	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	124
292	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	125
293	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	126
294	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	127
295	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	128
296	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	129
297	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	130
298	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	131
299	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	132
300	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	133
301	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	134
302	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	135
303	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	136
304	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	137
305	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	138
306	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	139
307	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	140
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309	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	142
310	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	143
311	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	144
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320	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	153
321	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	154
322	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	155
323	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	156
324	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	157
325	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	158
326	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	159
327	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	160
328	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	161
329	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	162
330	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	163
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336	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	169
337	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	170
338	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	171
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340	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	173
341	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	174
342	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	175
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348	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	181
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358	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	191
359	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	192
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361	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	194
362	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
363	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	196
364	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	197
365	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	1998
366	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
367	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	200
368	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	201
369	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	202
370	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	203
371	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	204
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TABLE II: Parameters used for each step of EST analysis

		Search Charac	teristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S-61 X-16	90	17
tRNA	Fasta	both		80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both	•	70	40
L1	Blastn	both	S-72	70	40
Repeats	Biastn	both	S=72	70	40
Promoters	Blastn	top	S=54 X=16	90	15⊥
Vertebrate	fasta*	both	S=108	90	30
ESTs	Blatsn	both	S-108 X-16	90	30
Proteins	blastxŋ	top	E-0.001		

^{*} use "Quick Fast" Database Scanner

 $^{\,\}perp\,$ alignment further constrained to begin closer than 10bp to EST\5' end

⁵ η using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

Search characteristics			Selection characteristics			
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous •	FASTA	both	•	90	15	
tRNA*	FASTA	both		80	90	1
rRNA*	BLASTN	both	S-108	80	40	
mtRNA*	BLASTN	both	S-108	80	40	· · · · · · · · · · · · · · · · · · ·
Procaryotic ¹	BLASTN	both	S-144	90	40	
Fungal*	BLASTN	both	S-144	90	40	
Alu*	BLASTN	both	S-72	70	40	max 5 matches, masking
L11	BLASTN	both	S-72	70	40	max 5 matches, masking
Repeats!	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides
Polyadenylati on signal	•	top	AATAAA allowing 1 mis	match		in the 50 nucleotides preceding the 5' end of the polA
Vertebrate*	BLASTN then FASTA	both	·	90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs*	BLAST2N	both		90	30	
Geneseq	BLASTN	both	W-8, B-10	90	30	
ORF	BLASTP	top	W-8, B-10		•	on ORF proteins, max 10 matches
Proteins*	BLASTX	top	E-0.001	70	30	

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

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TABLE IV

	- COO.					
ld	FCS Location	SigPep Location	Mature Polypeptide	Stop Codon	PolyA Signal	PolyA Site Location
<u> </u>			Location	Location	Location	
40	7 through 471	7 through 99	100 through 471	472	537 through 542	554 through 568
41	168 through 332	·	168 through 332	333	557 through 562	
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614		
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041		2024 through 2036
46	443 through 619	443 through 589	590 through 619	620		1267 through 1276
47	206 through 747		206 through 747	1		1.
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41	·	21 through 41	42	328 through 333	357 through 370
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994
52	271 through 399	·	271 through 399	400	 	
53	103 through 252	103 through 213	214 through 252	253		588 through 597
54	2 through 460	•	2 through 460	461	713 through 718	735 through 748
55	31 through 231	•	31 through 231	232	769 through 774	690 through 703
56	305 through 565	•	305 through 565	566	694 through 699	713 through 725
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705
58	135 through 206	·	135 through 206	207	850 through 855	1056 through 1069
59	135 through 818	·	135 through 818	819	909 through 914	1071 through 1084
60	33 through 290	33 through 92	93 through 290	291		1.
61	485 through 616	·	485 through 616	617		669 through 682
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312		
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
58	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
59	2 through 757	2 through 205	206 through 757	758	 	1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285
1	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
2	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
3	62 through 916	62 through 757	758 through 916			904 through 916
4	62 through 520		62 through 520	521	1124 through 1129	1141 through 1153
5	21 through 167	•	21 through 167	168		
6	22 through 318		94 through 318	319	497 through 502	516 through 526
7	8 through 292		119 through 292	293	317 through 322	339 through 352
8	16 through 378		85 through 378	379	502 through 507	522 through 542

CON	T. TABLE IV					
79	57 through 233	•	57 through 233	1.	·	•
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542	·	597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382	·	89 through 382	- 383	•	408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362		
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802		199 through 802	 	780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361	·	26 through 361	·		350 through 361
92	3 through 131	·	3 through 131	132		591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417		327 through 417			404 through 417
97	63 through 398	63 through 206	207 through 398	399		
98	2 through 163		2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466	·	
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295	1.	
102	81 through 518	81 through 173	174 through 518	519		
103	66 through 326	·	66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290	·	1.
105	36 through 497	·	36 through 497	498	650 through 655	663 through 685
106	18 through 320		18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333	•	702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563	 . 	
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400	· .	
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	
119	44 through 505	44 through 223	224 through 505	506		 .
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770
			•	L	l	1

CON	IT. TABLE IV					
121	58 through 1095	58 through 114	115 through 1095	1096	•	1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659	•	440 through 659	1.	601 through 606	•
127	38 through 283	38 through 85	86 through 283	284	257 through 262	·
128	121 through 477	121 through 288	289 through 477	· · · · · ·	•	
129	2 through 163	•	2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62.through 385	•	62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551		714 through 725
133	124 through 231	·	124 through 231	232	·	387 through 400
134	131 through 1053	131 through 169	170 through 1053	· -	1019 through 1024	
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382	•	875 through 886
138	46 through 579	46 through 156	157 through 579	580	· · · · · · · · · · · · · · · · · · ·	
139	92 through 471	92 through 172	173 through 471		454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559	·	1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674	•	1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263					,	, {

CONT. TABLE IV

COV	IT. TABLE IV					
264	42 through 299	42 through 101	102 through 299	300	·	762 through 775
265	198 through 431	198 through 260	261 through 431	432	•	1064 through 1074
266	279 through 473	279 through 362	363 through 473	474	944 through 949	970 through 981
267	12 through 644	12 through 92	93 through 644	645	1002 through 1007	1020 through 1031
268	91 through 459	91 through 330	331 through 459	460		1271 through 1281
269	70 through 327	70 through 147	148 through 327	328	1741 through 1746	1763 through 1774
270	12 through 497	12 through 104	105 through 497	498	935 through 940	955 through 967
271	90 through 383	90 through 200	201 through 383	384	609 through 614	632 through 643
272	332 through 541	332 through 376	377 through 541	542	739 through 744	761 through 773
273	43 through 222	43 through 177	178 through 222	223	530 through 535	555 through 566
274	115 through 231	115 through 180	181 through 231	232	419 through 424	445 through 455
275	232 through 384	232 through 300	301 through 384	385	650 through 655	662 through 673
276	143 through 427	143 through 286	287 through 427	428	606 through 611	628 through 639
277	284 through 463	294 through 379	380 through 463	464	·	762 through 772
278	162 through 671	162 through 398	399 through 671	672	805 through 810	830 through 840
279	63 through 632	63 through 308	309 through 632	633	808 through 813	829 through 840
280	21 through 362	21 through 200	201 through 362	363	821 through 826	838 through 849
281	21 through 503	21 through 344	345 through 503	504	1305 through 1310	1330 through 1341
282	1 through 201	1 through 63	64 through 201	202	637 through 642	660 through 671
283	39 through 1034	39 through 134	135 through 1034	1035	1566 through 1571	1587 through 1597
284	69 through 263	69 through 125	126 through 263	264	1173 through 1178	1196 through 1205
285	115 through 285	115 through 204	205 through 285	286	505 through 510	525 through 536
286	90 through 344	90 through 140	141 through 344	345	500 through 505	515 through 527
287	57 through 311	57 through 107	108 through 311	312	467 through 472	482 through 493
288	96 through 302	96 through 182	183 through 302	303	1	501 through 514
289	161 through 526	161 through 328	329 through 526	527		799 through 811
290	210 through 332	210 through 299	300 through 332	333	594 through 599	613 through 625
291	212 through 361	212 through 319	320 through 361	362	650 through 655	673 through 684
292	75 through 482	75 through 128	129 through 482	483	595 through 600	618 through 627
293	50 through 631	50 through 244	245 through 631	632	777 through 782	801 through 812
294	154 through 576	154 through 360	361 through 576	577	737 through 742	763 through 775
295	154 through 897	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
296	146 through 292	146 through 253	254 through 292	293	395 through 400	433 through 444
297	126 through 383	126 through 167	168 through 383 .	384	726 through 731	743 through 754
298	66 through 497	66 through 239	240 through 497	498	594 through 599	618 through 629
299	49 through 411	49 through 96	97 through 411	412	732 through 737	750 through 763
300	49 through 534	49 through 96	97 through 534	535	593 through 598	612 through 623
301	86 through 415	86 through 145	146 through 415	416	540 through 545	560 through 571
302	56 through 268	56 through 100	101 through 268	269	584 through 589	601 through 612
303	32 through 328	32 through 103	104 through 328	329	508 through 513	528 through 539
304	21 through 527	21 through 95	96 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374	375 through 647	648		668 through 681
						

CONT. TABLE IV

COI	NT. TABLE IV					•
306	262 through 471	262 through 306	307 through 471	472	663 through 668	682 through 693
307	74 through 1216	74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
308	48 through 164	48 through 89	90 through 164	165	482 through 487	505 through 517
309	185 through 334	185 through 295	296 through 334	335	355 through 360	392 through 405
310	195 through 347	195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
311	90 through 815	90 through 179	180 through 815	816	883 through 888	905 through 916
312	52 through 513	52 through 231	232 through 513	514	553 through 558	572 through 583
313	172 through 438	172 through 354	355 through 438	439	682 through 687	685 through 697
314	148 through 366	148 through 225	226 through 366	367	770 through 775	792 through 803
315	175 through 336	175 through 276	277 through 336	337		812 through 823
316	191 through 553	191 through 304	305 through 553	554	766 through 771	804 through 817
317	106 through 603	106 through 216	217 through 603	604	•	1102 through 1112
318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
320	44 through 814	44 through 112	113 through 814	815		978 through 989
321	3 through 581	3 through 182	183 through 581	582		1006 through 1016
322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
324	201 through 332	201 through 251	252 through 332	333		869 through 880
325	217 through 543	217 through 255	256 through 543	544	•	1206 through 1217
326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
331	672 through 752	672 through 722	723 through 752	753		1150 through 1161
332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645
334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400
335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
336	54 through 590	54 through 227	228 through 590	591	1.	955 through 965
337	133 through 846	133 through 345	346 through 846	847		890 through 901
338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347
339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983
340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745
341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106
342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190
343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070
344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213
345	86 through 709	86 through 361	362 through 709	710	943 through 948	963 through 973
346	63 through 320	63 through 179	180 through 320	321	771 through 776	799 through 810
347	299 through 418	299 through 379	380 through 418	419	739 through 744	762 through 771
					<u> </u>	

CONT. TABLE IV

	717 171000					
348	186 through 380	186 through 233	234 through 380	381	383 through 388	396 through 409
349	69 through 458	69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340		1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326	•	718 through 729
355	78 through 731	78 through 227	228 through 731	732	·	1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
357	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949	•	1016 through 1028
360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
361	628 through 804	628 through 711	712 through 804	805		864 through 875
362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
364	111 through 434	111 through 185	186 through 434	435	1.	618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613	1.	839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	633 through 644
369	9 through 185	9 through 50	51 through 185	186		906 through 918
370	14 through 316	14 through 121	122 through 316	317	442 through 447	458 through 471
371	70 through 1092	70 through 234	235 through 1092	1093	1475 through 1480	1493 through 1504
372	274 through 597	274 through 399	400 through 597	598	731 through 736	754 through 765
373	230 through 469	230 through 307	308 through 469	470	1004 through 1009	1027 through 1040
374	72 through 545	72 through 203	204 through 545	546		1151 through 1162
375	36 through 425	36 through 119	120 through 425	426	1215 through 1220	1240 through 1250
376	155 through 751	155 through 340	341 through 751	752	912 through 917	937 through 947
377	46 through 585	46 through 120	121 through 585	586	584 through 589	606 through 619
					I	

TABLE V

ld	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55	•	1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180	•	1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	1 through 97
151	1 through 7		
152	-42 through 157	-42 through -1	1 through 7
153	1 through 43	·	1 through 157
154	-37 through 13	-37 through -1	1 through 43
155	1 through 153		1 through 13
156	1 through 67		1 through 153
157	1 through 87	•	1 through 67 1 through 87
158	-85 through 165	-85 through -1	1 through 165
159	1 through 24	•	1 through 24
160	1 through 228	•	1 through 228
161	-20 through 66	-20 through -1	1 through 66
162	1 through 44		1 through 44
163	-58 through 256	-58 through -1	1 through 256
164	-80 through 9	-80 through -1	1 through 9
165	-15 through 83	-15 through -1	1 through 83
166	-36 through 56	-36 through -1	1 through 56
167	-16 through 335	-16 through -1	1 through 335
168	-47 through 91	-47 through -1	1 through 91
169	-73 through 28	-73 through -1	1 through 28
170	-68 through 184	-68 through -1	1 through 184
171	-68 through 282	-68 through -1	1 through 282
172	-68 through 322	-68 through -1	1 through 322
173	-82 through 108	-82 through -1	1 through 108
174	-232 through 53	-232 through -1	1 through 53
175	1 through 153		1 through 153
176	1 through 49		1 through 49
177	-24 through 75	-24 through -1	1 through 75
178	-37 through 58	-37 through -1	1 through 58
179	-23 through 98	-23 through -1	1 through 98
180	1 through 59		1 through 59
181	-14 through 72	-14 through -1	1 through 72
182	-58 through 107	-58 through -1	1 through 107
183	-35 through 45	-35 through -1	
184	-21 through 52	-21 through -1	1 through 45 1 through 52
185	1 through 98		1 through 52 1 through 98
186	-21 through 91	-21 through -1	
187	-44 through 26	-44 through -1	1 through 91
188	-13 through 79	-13 through -1	1 through 26
189	-42 through 165	-42 through -1	1 through 79
190	1 through 201		1 through 165 1 through 201

CONT. TABLE V

CONT. TABL	E V		••
191	-37 through 342	-37 through -1	1 through 342
192	1 through 112		1 through 342
193	1 through 43		1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	1 through 319
197	1 through 30	· ·	
198	-48 through 64	-48 through -1	1 through 30
199	1 through 54	40 through 1	1 through 64
200	-21 through 130	-21 through -1	1 through 54
201	-25 through 203	-25 through -1	1 through 130
202	-47 through 17	-47 through -1	1 through 203
203	-31 through 115	-31 through -1	1 through 17
204	1 through 87	-51 through -1	1 through 115
205	-27 through 13	27 through 1	1 through 87
206	1 through 154	-27 through -1	1 through 13
207	1 through 101		1 through 154
208	-22 through 434	20.4	1 through 101
209	-17 through 81	-22 through -1	1 through 434
210	-29 through 54	-17 through -1	1 through 81
211	-23 through 206	-29 through -1	1 through 54
212		-23 through -1	1 through 206
213	-21 through 131 -54 through 125	-21 through -1	1 through 131
214	-92 through 177	-54 through -1	1 through 125
215	-22 through 113	-92 through -1	1 through 177
216		-22 through -1	1 through 113
217	-38 through 29 -54 through 71	-38 through -1	1 through 29
218	-21 through 355	-54 through -1	1 through 71
219		-21 through -1	1 through 355
220	-30 through 181	-30 through -1	1 through 181
221	-60 through 94	-60 through -1	1 through 94
222	-42 through 81	-42 through -1	1 through 81
223	-19 through 327	-19 through -1	1 through 327
224	-20 through 190	-20 through -1	1 through 190
225	-20 through 164	-20 through -1	1 through 164
	-22 through 205	-22 through -1	1 through 205
226	-41 through 33	-41 through -1	1 through 33
227	1 through 73		1 through 73
228	-16 through 66	-16 through -1	1 through 66
229	-56 through 63	-56 through -1	1 through 63
230	1 through 54	•	1 through 54
231	-14 through 196	-14 through -1	1 through 196
232	1 through 108	•	1 through 108
233	-18 through 25	-18 through -1	1 through 25
234	1 through 36		1 through 36
235	-13 through 294	-13 through -1	1 through 294
236	-32 through 74	-32 through -1	1 through 74
237	-19 through 23	-19 through -1	1 through 23
238	-20 through 97	-20 through -1	1 through 97
239	-37 through 141	-37 through -1	1 through 141
240	-27 through 99	-27 through -1	1 through 99
241	-115 through 59	-115 through -1	1 through 59
378	-20 through 32	-20 through -1	1 through 32
		· · · · · · · · · · · · · · · · · · ·	, , , , , , , , , , , , , , , , , , ,
379 380	-23 through 170	-23 through -1	1 through 170

ONT. TABLE V			
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	-18 through -1	1 through 42
397	-93 through 99	∙93 through ∙1	1 through 99
398	-72 through 77	-72 through -1	1 through 77
399	-20 through 53	-20 through -1	1 through 53
400	-20 through 66	-20 through -1	1 through 66
401	-21 through 57	-21 through -1	1 through 57
402	-28 through 37	-28 through -1	1 through 37
403	-27 through 184	-27 through -1	1 through 184
404	-80 through 43	-80 through -1	1 through 43
405	-26 through 60	-26 through -1	1 through 60
406	-31 through 131	-31 through -1	1 through 131
407	-37 through 61	-37 through -1	1 through 61
408	-15 through 55	-15 through -1	1 through 55
409	-45 through 15	-45 through -1	1 through 15
410	-22 through 17	-22 through -1	1 through 17
411	-23 through 28	-23 through -1	1 through 28
412	-48 through 47	-48 through -1	1 through 47
413	-32 through 28	-32 through -1	1 through 28
414	-79 through 91	-79 through -1	1 through 91
415	-82 through 108	-82 through -1	1 through 108
416	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
418	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
420	-19 through 46	-19 through -1	1 through 46
422	-30 through 27	-30 through -1	1 through 27
423	-17 through 68	-17 through -1	
424	-17 through 68	-17 through -1	1 through 68 1 through 68
425	-29 through 40	-29 through -1	
426	-56 through 66	-56 through -1	1 through 40
427	-30 through 11	-30 through -1	1 through 66
428	-36 through 14		1 through 11
429	-18 through 118	-36 through -1	1 through 14
430	-18 through 118	-18 through -1	1 through 118
431		-65 through -1	1 through 129
431	-69 through 72	-69 through -1	1 through 72
432	-69 through 179	-69 through -1	1 through 179
	-36 through 13	-36 through -1	1 through 13
434	-14 through 72	-14 through -1	1 through 72
435	-58 through 86	-58 through -1	1 through 86

CONT. TARLE V

ONT. TABLE V			
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	·76 through 91	.76 through -1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	·14 through 25	-14 through -1	
446	-37 through 13	-37 through -1	1 through 25 1 through 13
447	-26 through 25	-26 through -1	
448	-30 through 212	-30 through -1	1 through 25
449	-60 through 94	-60 through -1	1 through 212
450	-61 through 28	-61 through -1	1 through 94
451	-26 through 47	-26 through -1	1 through 28
452	-34 through 20	-34 through -1	1 through 47
453	-38 through 83	-38 through -1	1 through 20
454	-37 through 129	-37 through -1	1 through 83
455	-26 through 154	-26 through -1	1 through 129
456	-64 through 27		1 through 154
457	-23 through 234	-64 through -1 -23 through -1	1 through 27
458	-60 through 133	-60 through -1	1 through 234
459	-28 through 79		1 through 133
460	-13 through 108	-28 through -1	1 through 79
461	-17 through 27	-13 through -1	1 through 108
462	-13 through 96	-17 through -1	1 through 27
463	-41 through 102	-13 through -1	1 through 96
464	-30 through 202	-41 through -1 -30 through -1	1 through 102
465	-21 through 40	-21 through -1	1 through 202
466	-19 through 15	-19 through -1	1 through 40
467	-54 through 161	-54 through -1	1 through 15
468	-17 through 10	-17 through -1	1 through 161
469	-24 through 61	-24 through -1	1 through 10
470	-16 through 35	-16 through -1	1 through 61
471	-43 through 24		1 through 35
472	-15 through 48	-43 through -1	1 through 24
473	-58 through 121	-15 through -1	1 through 48
474	-71 through 167	-58 through -1 -71 through -1	1 through 121
475	-37 through 141	-71 through -1	1 through 167
476	-21 through 75		1 through 141
477	-24 through 17	-21 through -1	1 through 75
478	-27 through 86	-24 through -1	1 through 17
479	-18 through 232	-27 through -1	1 through 86
480		-18 through -1	1 through 232
481	-21 through 130 -25 through 214	-21 through -1	1 through 130
482	-25 through 214 -92 through 116	-25 through -1	1 through 214
483		-92 through -1	1 through 116
484	-39 through 47	-39 through -1	1 through 47
484	-27 through 13	-27 through -1	1 through 13
	-16 through 49	-16 through -1	1 through 49
486	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	· 1 through 15

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490	-52 through 111	-52 through -1	1 showsh 111
491	-47 through 17	-47 through -1	1 through 111
492	-50 through 168	-50 through -1	1 through 17
493	-15 through 201	-15 through -1	1 through 168
494	-19 through 115	-19 through -1	1 through 201
495	-16 through 69	-16 through -1	1 through 115
496	-29 through 263	-29 through -1	1 through 69
497	-56 through 66		1 through 263
498	-28 through 31	-56 through -1	1 through 66
499	-13 through 86	-28 through -1	1 through 31
500	-13 through 86	-13 through -1	1 through 86
501	-15 through 83	-13 through -1	1 through 86
502		-25 through -1	1 through 83
503	-15 through 168	-15 through -1	1 through 168
503	-15 through 83	-15 through -1	1 through 83
	-57 through 126	-57 through -1	1 through 126
505	-14 through 126	-14 through -1	1 through 126
506	-14 through 45	-14 through -1	1 through 45
507	-36 through 65	-36 through -1	1 through 65
508	-55 through 286	-55 through -1	1 through 286
509	-42 through 66	-42 through -1	1 through 66
510	-26 through 54	-26 through -1	1 through 54
511	-44 through 114	-44 through -1	1 through 114
512	-28 through 102	-28 through -1	1 through 102
513	-62 through 137	-62 through -1	1 through 137
514	-25 through 155	-25 through -1	i anough 137

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TABLE VI

ld	Collection refs	Deposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 98921	SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
56	ATCC # 98920	SignalTag 67-90
7	ATCC # 98921	SignalTag 121-144
58	ATCC # 98920	SignalTag 67-90
59	ATCC # 98920	SignalTag 67-90
30	ATCC # 98920	SignalTag 67-90
1	ATCC # 98923	SignalTag 44-66
2	ATCC # 98923	SignalTag 44-66
3	ATCC # 98923	SignalTag 44-66
4	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
5	ATCC # 98923	SignalTag 44-66
6	ATCC # 98921	SignalTag 121-144
7	ATCC # 98920	SignalTag 67-90
8	ATCC # 98920	SignalTag 67-90
9	ATCC # 98921	SignalTag 121-144
)	ATCC # 98921	SignalTag 121-144
1	ATCC # 98921	SignalTag 121-144
2	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
3	ATCC # 98923	SignalTag 44-66

74	ATCC # 98923	SignalTag 44-66	_
75	ATCC # 98920	SignalTag 67-90	
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
78	ATCC # 98921	SignalTag 121-144	
79	ATCC # 98923	SignalTag 44-66	_
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	_
81	ATCC # 98921	SignalTag 121-144	
82	ATCC # 98920	SignalTag 67-90	
83	. ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
84	ATCC # 98923	SignalTag 44-66	
85	ATCC # 98923	SignalTag 44-66	
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
87	ATCC # 98923	SignalTag 44-66	
88	ATCC # 98923	SignalTag 44-66	_
89	ATCC # 98923	SignalTag 44-66	_
90	ATCC # 98923	SignalTag 44-66	
91	ATCC # 98923	SignalTag 44-66	٦
92	ATCC # 98920	SignalTag 67-90	٦
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	٦
94	ATCC # 98923	SignalTag 44-66	
95	ATCC # 98923	SignalTag 44-66	٦
96	ATCC # 98920	SignalTag 67-90	٦
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	٦
98	ATCC # 98921	SignalTag 121-144	7
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	┨
100	ATCC # 98921	SignalTag 121-144	7
101	ATCC # 98920	SignalTag 67-90	7
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	7
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	7
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	↿
105	ATCC # 98921	SignalTag 121·144	7
106	ATCC # 98920	SignalTag 67-90	1
107	ATCC # 98920	SignalTag 67-90	7
108	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	7
109	ATCC # 98923	SignalTag 44-66	7
10	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	1

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111	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120.
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998 .
139	ECACC # 98121506	SignalTag 11121998
140	ECACC # 98121506	SignalTag 11121998

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TABLE VII

Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CL0_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22-11-2-H9-CL1_1	43	DNA
25-7-3-D4-CL0_2	44	DNA
26-27-3-D7-CL0_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CL0_1	48	DNA
27-1-2-B3-CL0_2	49	DNA
27-19-3-G7-CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	. DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	·65	DNA
47-14-1-C3-CLO_5	66	DNA
47-15-1-E11-CL0_1	67	DNA
47-15-1-H8-CLO_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48-1-1-H7-CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2_1	73	DNA

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48-54-1-G9-CL3_1	74	DNA
48-7-4-H2-CL2_2	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-G9-CLO_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CL0_2	82	DNA
51-34-3-F8-CLO_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	87	DNA
58-34-3-C9-CL1_2	88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CLO_1	98	DNA
77-16-4-G3-CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CLO_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CLO_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CLO_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CLO_3	110	DNA

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30-12-3-G5-CL0_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CLO_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3:CLO_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CLO_2	145	PRT
26-27-3-D7-CL0_1	146	PRT
26-35-4-H9-CL1_1	147	PRT

26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CLO_5	167	PRT
47-15-1-E11-CLO_1	168	PRT
47-15-1-H8-CL0_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CLO_5	172	PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51-15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRT
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CLO_2	183	PRT
51-34-3-F8-CLO 2	184	PRT

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57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CL0_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CL0_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CLO_3	211	PRT
30-12-3-G5-CLO_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214.	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CLO_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CLO_4	221	PRT

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57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224	PRT
78-8-3-E6-CLO_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33-11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLO_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CL0_1	233	PRT
55-1-3-D11-CL0_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT
78-21-3-G7-CL2_1	240	PRT
58-45-4-B11-CL13_2	241	PRT
20-6-1-D11-FL2	242	DNA
20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1-G11-FL1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
33-14-4-E1-FL1	256	DNA
33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA

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33-27-1-E11-FL1	259	DNA	
33-28-4-D1-FL1	260	DNA	
33-28-4-E2-FL2	261	DNA	
33-30-4-C4-FL1	262	DNA	
33-35-4-F4-FL1	263	DNA	
33-36-3-F2-FL2	264	DNA	
33-52-4-F9-FL2	265	DNA	
33-52-4-H3-FL1	266	DNA	
33-59-1-B7-FL1	267	DNA	
33-71-1-A8-FL1	268	DNA	
33-72-2-B2-FL1	269	DNA	
33-105-2-C3-FL1	270	DNA	
33-107-4-C3-FL1	271	DNA	
33-110-2-64-FL1	272	DNA	
47-7-4-D2-FL2	273	DNA	
47-10-2-G12-FL1	274	DNA	
47-14-3-D8-FL1	275	DNA	
47-18-3-C2-FL1	276	DNA	
47-18-3-G5-FL2	277	DNA	
47-18-4-E3-FL2	278	DNA	
48-3-1-H9-FL3	279	DNA	
48-4-2-H3-FL1	280	DNA	
48-6-1-C9-FL1	281	DNA	
48-7-4-H2-FL2	282	DNA	
48-8-1-D8-FL3	283	DNA	
48-13-3-H8-FL1	284	DNA	
48-19-3-A7-FL1	285	DNA	
48-19-3-G1-FL1	286	DNA	
48-25-4-D8-FL1	287	DNA	
48-21-4-H4-FL1	288	DNA	
48-26-3-B8-FL2	289	DNA	
48-29-1-E2-FL1	290	DNA	
48-31-3-F7-FL1	291	DNA	
48-47-3-A5-FL1	292	DNA	
51-1-1-G12-FL1	293	DNA	
51-1-4-E9-FL3	294	DNA	
51-1-4-E9-FL2	295	DNA	
			

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51-2-1-E10-FL1	296	DNA
51-2-3-F10-FL1	297	DNA
51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
51-3-3-B10-FL3	300	DNA
51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
51-15-4-H10-FL1	305	DNA
51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
55-1-3-H10-FL1	314	DNA
55-5-4-A6-FL1	315	DNA
58-26-3-D1-FL1	316	DNA
57-18-1-D5-FL1	317	DNA
57-27-3-A11-FL1	318	DNA
57-27-3-G10-FL2	319	DNA
58-10-3-D12-FL1	320	DNA
58-11-1-G10-FL1	321	DNA
58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
58-38-1-A2-FL2	324	DNA
58-38-1-E5-FL1	325	DNA
58-44-2-B3-FL3	326	DNA
58-45-3-H11-FL1	327	DNA
58-53-2-B12-FL2	328	DNA
59-9-4-A10-FL1	329	DNA
60-16-3-A6-FL1	330	DNA
60-17-3-G8-FL2	331	DNA
62-5-4-B10-FL1	332	DNA

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65-4-4-H3-FL1	333	DNA
74-3-1-B9-FL1	334	DNA
76-4-1-G5-FL1	335	DNA
76-7-3-A12-FL1	336	DNA
76-16-4-C9-FL3	337	DNA
76-30-3-B7-FL1	338	DNA
77-5-1-C2-FL1	339	DNA
77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
78-16-2-C2-FL1	348	DNA
78-18-3-B4-FL3	349	DNA
78-20-1-G11-FL1	350	DNA
78-22-3-E10-FL1	351	DNA
78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4-G8-FL3	365	DNA
33-97-4-G8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA

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57-25-1-F10-FL2	370	DNA	
58-19-3-D3-FL1	371	DNA	
58-34-3-C9-FL2	372	DNA	
58-48-4-E2-FL2	373	DNA	
76-21-1-C4-FL1	374	DNA	
78-26-2-H7-FL1	375	DNA	
77-20-2-E11-FL1	376	DNA	
47-1-3-F7-FL2	377	DNA	
20-6-1-D11-FL2	378	PRT	
20-8-4-A11-FL2	379	PRT	
22-6-2-C1-FL2	380	PRT	
22-11-2-H9-FL1	381	PRT	
23-8-3-B1-FL1	382	PRT	
24-3-3-C6-FL1	383	PRT	
24-4-1-H3-FL1	384	PRT	
26-45-2-C4-FL2	385	PRT	
26-48-1-H10-FL1	386	PRT	
26-49-1-A5-FL2	387	PRT	
30-6-4-E3-FL3	388	PRT	
33-6-1-G11-FL1	389	PRT	
33-8-1-A3-FL2	390	PRT	
33-11-3-C6-FL1	391	PRT	
33-14-4-E1-FL1	392	PRT	
33-21-2-D5-FL1	393	PRT	
33-26-4-E10-FL1	394	PRT	
33-27-1-E11-FL1	395	PRT	
33-28-4-D1-FL1	396	PRT	
33-28-4-E2-FL2	397	PRT	
33-30-4-C4-FL1	398	PRT	
33-35-4-F4-FL1	399	PRT	
33-36-3-F2-FL2	400	PRT	
33-52-4-F9-FL2	401	PRT	
33-52-4-H3-FL1	402	PRT	
33-59-1-B7-FL1	403	PRT	
33-71-1-A8-FL1	404	PRT	
33-72-2-B2-FL1	405	PRT	
33-105-2-C3-FL1	406	PRT	

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33-107-4-C3-FL1	407	PRT
33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
. 48-4-2-H3-FL1	416	PRT
48-6-1-C9-FL1	417	PRT
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	425	PRT
48-29-1-E2-FL1	426	PRT
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
51-2-1-E10-FL1	432	PRT
51-2-3-F10-FL1	433	PRT
51-2-4-F5-FL1	434	PRT
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	PRT
51-7-3-G3-FL1	437	PRT
51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	PRT

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51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
58-26-3-D1-FL1	452	PRT
57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
59-9-4-A10-FL1	465	PRT
60-16-3-A6-FL1	466	PRT
60-17-3-G8-FL2	467	PRT
62-5-4-B10-FL1	468	PRT
65-4-4-H3-FL1	469	PRT
74-3-1-B9-FL1	470	PRT
76-4-1-G5-FL1	471	PRT
76-7-3-A 12-FL1	472	PRT
76-16-4-C9-FL3	473	PRT
76-30-3-B7-FL1	474	PRT
77-5-1-C2-FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT

77-26-2-F2-FL3	481	PRT
78-6-2-E3-FL2	482	PRT
78-7-1-G5-FL2	483	PRT
78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT-
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-86-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-83-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3-C9-FL2	508	PRT
58-48-4-E2-FL2	509	PRT
76-21-1-C4-FL1	510	PRT
78-26-2-H7-FL1	511	PRT
77-20-2-E11-FL1	512	PRT
47-1-3-F7-FL2	513	PRT

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TABLE VIII

ID	Locations	PROSITE Signature Name		
195	110-121	Aldehyde dehydrogenases csyteine active site		
221	28-37	ATP synthase alpha and beta subunits signature		
223	171-181	Regulator of chromosome condensation (RCC1) signature 2		
225	90-112	Phosphatidylethanolamine-binding protein family signature		
226	10-34	Protein kinases ATP-binding region signature		

WHAT IS CLAIMED IS:

- A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242 377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of 5 SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
 - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID Nos: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48,
 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- 5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.
 - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEO ID NOs: 141-241 and 378-513.
- A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20
 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID Nos: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
 - 9. A purified or isolated protein comprising the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
 - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said cDNA.

- 5 14. The method of Claim 13, further comprising the step of isolating said protein.
 - 15. A protein obtainable by the method of Claim 14.
 - 16. A host cell containing a recombinant nucleic acid of Claim 1.
 - 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- 19. A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
 - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

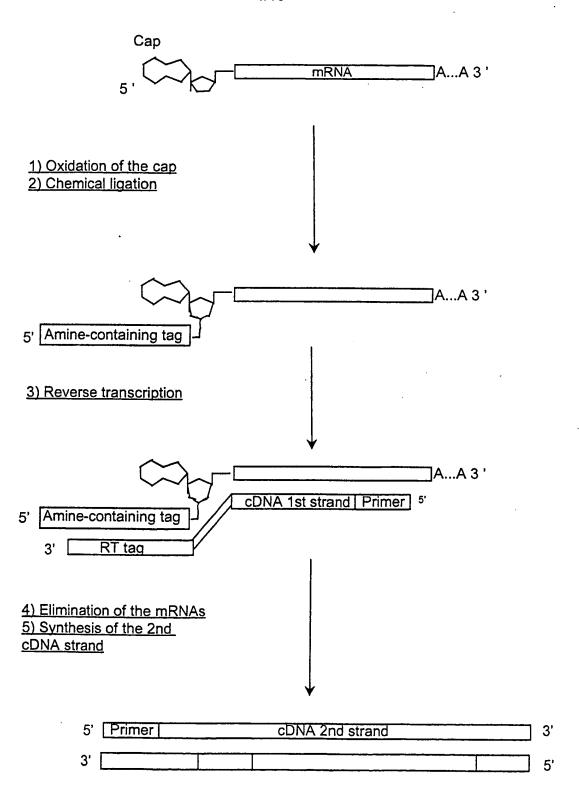
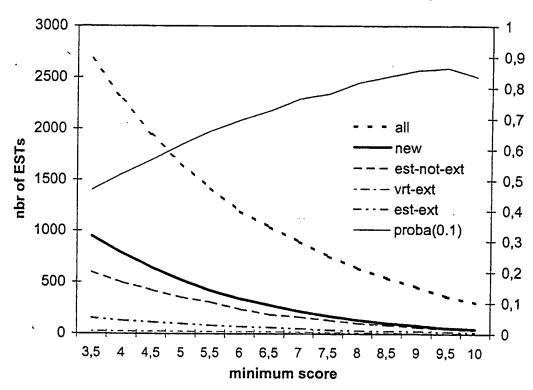


Figure 1

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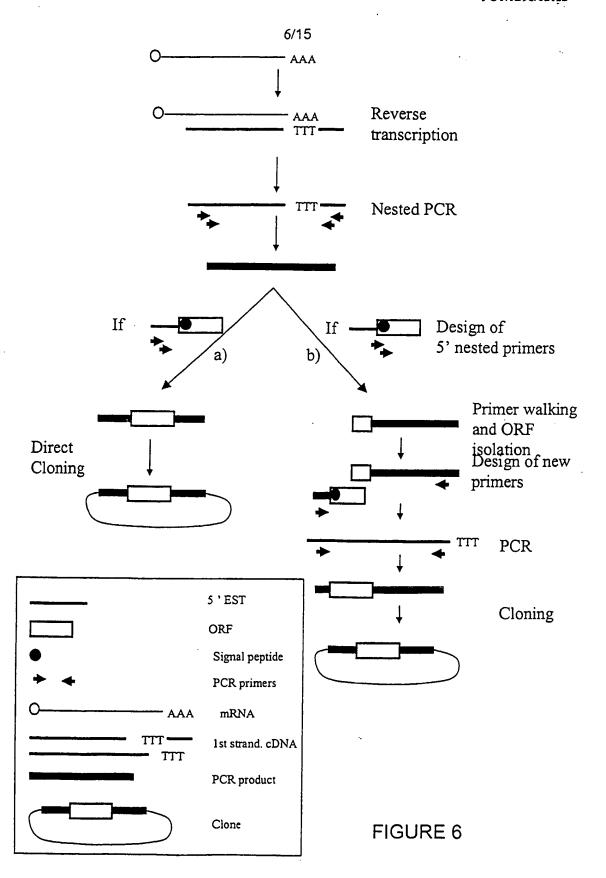
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3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

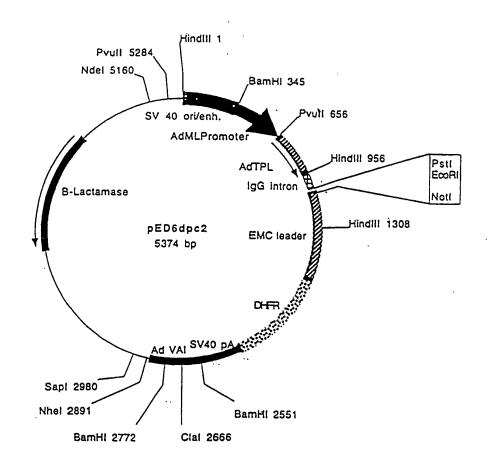
influence of minimum score on signal peptide recognition



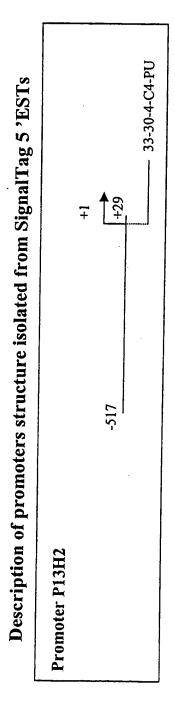
Minimum signal peptide score		New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	- 21	96
5,5	1417	419	307	19	80
6	1190	340	238	.18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	. 63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

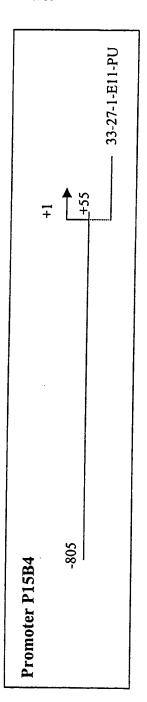
	1				
	•		ESTs	ESTs	ESTs
	1		matching	extending	extending
Tissue	All ESTs	New ESTs	public EST	known	public EST
1			closer than	mRNA more	
			40 bp from	than 40 bp	bp
Brain	329	404	beginning		
I .	329 134	131	75	3	24
Cancerous prostate Cerebellum		40	37	1	6
Colon	17	9	1	0	6
	21	11	4	0	0
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	0
Heart	30	15	7	0	1
Hypertrophic prostate	8 6	23	22	2	2
Kidney	10	7	3	0	0
Large intestine	21	8	4	0	1
Liver	23	9	6	0	0
Lung	24	12	4	. 0	1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	0
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	ŏ
Testis	131	68	25	1	
Thyroid	17	8	2	0	2
Umbilical cord	55	17	12	1	8 2 3 2
Uterus	28	15	3	Ó	3
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150
<u> </u>		U 11	001	20	130





Plasmid name: pED6dpc2 Plasmid size: 5374 bp 8/15





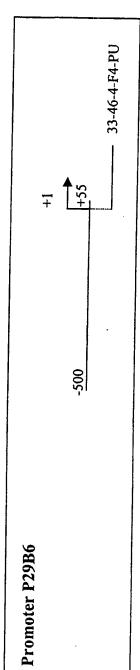


FIGURE 8

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Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501		0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	11	GCACACCTCAG
GATA_C	-364	-	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	•	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	. +	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	•	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	•	0.986	8	AGAGGGGA

Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	•	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	. 8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

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100.0% identity in 125 aa overlap 30 40 SEQ ID NO: 217 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA 20 . 30 90 100 120 70 80 110 SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD 80 90 100 110

SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

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CLUSTAL W(1.5) multiple sequence alignment

SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	KGESQVFKKAVVLHVLPEEPKGTQMLTKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	IVFRYYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN VTRRKHHCVREGSG
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	GNKSSVNSTVLVKNTKKTNP

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99.6% identity in 225 aa overlap SEQ ID NO: 515 PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 231 LRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 515 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 231 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 515 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 231 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 515 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 231 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR

250 260
SEQ ID NO: 515 HFPNEFIVETKICQE

SEQ ID NO: 231 HFPNEFIVETKICQE

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99.7% identity in 353 aa overlap SEQ ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY 70 . SEO ID NO:196 DVFGDPAYLOLAHGYVKOSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKOAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCOLKF SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL

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98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEO ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSODPEOHLTELREPAPGTNOROPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL

SEQ ID NO:519 AS

SEQ ID NO:158 PP

FIGURE 14

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68.9% identity in 74 aa overlap

20 30 40 50 10 SEQ ID NO:226 MIARRNPVPLRFLPDEARSLPPPKLTDPRLLYIGFLGYCSGLIDNLIRRRPIATAGLHR 1...... ${\tt SEQ~ID~NO:514~MMTGRQGRATFQFLPDEARSLPPPKLTDPRLAFVGFLGYCSGLIDNAIRRRPVLLAGLHR}$

10 20 30 40

60

SEQ ID NO:226 QLLYITAFFLLDIIL

SEQ ID NO:514 QLLYITSFVFVGYYLLKRQDYMYAVRDHDMFSYIKSHPEDFPEKDKKTYGEVFEEFHPVR . 80 90

70

100

110

. WO 99/31236 PCT/IB98/02122

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 Bougueleret, Lydie

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georgeogra geogetatea agaateerea accorrecto accadageon accorre	
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Met Trp Trp Phe	
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Ala Ala Phe Ile Phe Ser Tyr Ile Thr Ala Val Thr Leu His His Ile	
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Asp Pro Ala Leu Pro Tyr Ile Ser Asp Thr Gly Thr Val Ala Pro Xaa	
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and can con acc aga acc not one and acc acc acc acc and	J47
Lys Cys Leu Phe Gly Ala Met Leu Asn Ile Ala Ala Val Leu Cys Gln	
35 40 45	602
and taganations guaration of the control of the con	502
Lys ctcttcaraa acatotottt acaaocatat ctcttgtatt gctttctaca ctgttgaatt	662

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722

782

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Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
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Ala Leu Leu Leu Pro His Cys Gln Lys Pro Phe Val Tyr Asp Leu His  1 5 10 15	
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52

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Ile Lys Ser Ser Pro Val Phe Gln Ile Pro Lys Asn Asp Asp Ile Pro 5 10 15 20	
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His
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Arg Arg Pro Arg I	Leu Gly Arg Cys	Ser Asp Met Asp Thr Ala Arg Thr	
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521 568

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Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn 230 235 cag tee tte ege ate ace ate ett eeg cag caa tae etg egg eea gtg 819 Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val 245 250 867 gaa gat gtg gcc acg tcc caa gac gac tgt tac aag ttt gcc atc tca Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser 265 260 915 cag toa too acg ggc act gtt atg gga gct gtt atc atg gag ggc ttc Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe 285 280 275 963 tac gtt gtc ttt gat cgg gcc cga aaa cga att ggc ttt gct gtc agc Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser 295 300 290 get tgc cat gtg cac gat gag ttc agg acg gca gcg gtg gaa ggc cen 1011 Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro 310 315 1059 ttt tgt cac ctt gga cat gga aga ctg tgg cta caa cat tcc aca gac Phe Cys His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp 330 325 aga tgagtcaacc ctcatgacca tagcctatgt catggctgcc atctgcgccc 1112 Arq tottcatgct gccactctgc ctcatggtgt gtcagtggcg ctgcctccgc tgcctgcgcc 1172 agcagcatga tgactttgct gatgacatct ccctgctgaa gtgaggaggc ccatgggcag 1232 1292 aagataggga ttcccctgga ccacacctcc gtggttcact ttggtcacaa gtaggagaca cagatggcac ctgtggccag agcacctcag gaccctcccc acccaccaaa tgcctctgcc 1352 1412 ttgatggaga aggaaaaggc tggcaaggtg ggttccaggg actgtacctg taggagacag aaaagagaag aaagaagcac tctgctggcg ggaatactct tggtcacctc aaatttaagt 1472 cgggaaattc tgctgcttga aacttcagcc ctgaaccttt gtcaccattc ctttaaattc 1532 tccaacccaa agtattcttc ttttcttagt ttcagaagta ctggcatcac acgcaggtta 1592 1652 gccaaagtca gtaggagagg atgcacagtt tgctatttgc tttagagaca gggactgtat 1712 1747 aaacaagcct aacattggtg caaaaaaaaa aaaaa

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				1				5					10			202
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		15					20					25			~~~	350
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Tyr		Ala	Gly	Ile	Glu		Leu	His	GIn	гÀа	40	GIU	neu	PIO	Map	
	30					35					-	act	tat	atc	tet	398
aat	gta	tcc	.ggt	gaa	דננ	gga	rgg m-m	COC	Dhe	Cyc	T.en	Ala	Cve	Val	Ser	•••
	Val	ser	GIĀ	Glu		GIÀ	irb	261	Pile	55	neu	ALU	Cyb		60	
45				ttc	50	act	+~+	act	ctc		atc	taa	act	act		446
gct	CCC	tta	Cag	Phe	Mat	Ala	Ser	Mla	Len	Phe	Ile	Tro	Ala	Ala	His	
Ala	PIO	Leu	GIII	65	MEL	AIG	SCI	n.u	70					75		
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Thr	Acn	723	Ara	Glu	Tvr	Thr	Leu	Met	Lvs	Ala	Tyr	Arg	Val	Āla		
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ata	attt	act	ttaa	qcqa	tq c	catc	tttc	a aa	taaa	ctaa	. tct	aggt	cta	gaca	gaaaga	731
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aat	acag	tgt	ttac	ttga	aa t	ttta	actt	t gt	aact	gcaa	gaa	10200	ayı	ttat	ccgggc	1211
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444	yaac	966	CCAC	cata	te S	accc acct	ator	15 as	·++=+	-t+c+	tat	aata	ata	taat	gtgcct	1451
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C C C		+2+	227	atat	.uu (taas	catt	o as	actt	aaaa	aac	ttat	tta	ttta	ttccac	1571
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tgc cgg aag tac tac ctg ggg ggg ttt gct ttc ttg cct ttt ctc tgg Cys Arg Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp -55 -50 -45	158
ttg gtc aac atc ttc tgg ttc tac cga gag gcc ttc ctt gtc cca gcc Leu Val Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala	206
tac aca gaa cag agc caa atc aaa ggc tat gtc tgg cgc tca gct gtg Tyr Thr Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val	254
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cag atc tac cgg ccc cgc tgg ggt gcc ctt ggg gac tac ctc tcc ttc Gln Ile Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe	350
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ggg Gly	Ala	Gln	Pro	Gln 1	Gln	Glu	Pro	Leu 5	Ala	Leu	Val	Phe	Arg 10	ttc Phe	GIÀ	241
Met	Ser	Gly 15	Ser	Phe	Gln	Leu	Val 20	Pro	Arg	Glu	Glu	Leu 25	Pro	cgc Arg	His	289
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Cys 45	ttc Phe	Val	Asp	Ile	Arg 50	Arg	Phe	Gly	Arg	Trp 55	Asp	Leu	Gly	gga Gly	Lys 60	385
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atc Ile	tgc Cys	gag Glu 95	acc	ctc Leu	ctg Leu	gac Asp	cag Gln 100	agg	ttc Phe	ttc Phe	aat Asn	ggc Gly 105	att Ile	ggc Gly	aac Asn	529
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cac	tcgo	gggc	aacc	gagag	gag g	rgga laact	ccat	g ca c to	caaaa	aget	. yaçı ı aaa	acco	ı	cact	gcactc	1174

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210 215	
and and and and act goa acc cag cod cot gag ggg acc age	913
Arg Asp Lett Pro Lys Arg Thr Ala Thr Gin Arg Pro Gid Giy ini ber	
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-35 -30 -25	193
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Ale new his here classical Classical Arg Lett Tie Lett Ser Pro Lett Pro	
Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro	
-20 -15 -10	241
-20 -15 -10 -10 -10 -10 -10 -10 -10 -10 -10 -10	241
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Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 75	403
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-45								+~+			3.55	+~~	~ 2 2	ato		248
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Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile	397
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352

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<220> <221> CDS <222> 8..292 <221> sig_peptide <222> 8..118 <223> Von Heijne matrix score 5.6 seg WLLLDALLRLGDT/KK <221> polyA signal <222> 317..322 <221> polyA_site <222> 339..352 <400> 77 ctgagat atg gca agt ccc gct gta aac agg tgg aaa agg cca agg ttg Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu -25 -30 -35 aag ccg gtg tgg cca cgg cgc ttg gaa tcc tgg ttg ttg ctg gat gct Lys Pro Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala -15 -10 ctt ttg cga tta gga gat acc aaa aaa aag cga cag cct gaa gca gcc Leu Leu Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala 1 -5 aca aaa too tgt gtt aga ago ago tgt ggg ggt coo agt gga gat ggg Thr Lys Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly 20 15 cet ecc eca tge etc eag eag ect gae ect egt gee etg tet eag geg Pro Pro Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala 30 35 ttc tct aga tcc ttt cct ctg ttt ccc tct ctc gct ggc aaa agt atg Phe Ser Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met

50

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Ile

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45

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<222> 522..542

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Lys Tyr Asn Leu I		gag tot tgc atc cgg aac ca Glu Ser Cys Ile Arg Asn Gl 15	ln Asp
tgc gag act ggc t	gc tgc caa cgt	gct cca gac aat tgc gag to Ala Pro Asp Asn Cys Glu Se 30 35	
		agt ctg tgt caa acg cag gt Ser Leu Cys Gln Thr Gln Va 50	
		tgc ctg cgg aac ctg act tg Cys Leu Arg Asn Leu Thr Cy 65	
tat tca aag aat g		agc atc gcc tat ggc cgt to Ser Ile Ala Tyr Gly Arg Cy 80	
aaa att gga agg o	ag aag ttg gct	aag aaa atg ttc ttc tagtgo Lys Lys Met Phe Phe 95	etece 388
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Ile Leu Cys Phe I 5 att caa gta ttg a	Leu Leu Pro His	His Arg Leu Gln Glu Ala Ar	l ga cag 107 rg Gln ga gaa 155
Ile Leu Cys Phe I 5 att caa gta ttg a Ile Gln Val Leu I 20 gag aga aaa caa a	Leu Leu Pro His  ag atg ctg cca  Lys Met Leu Pro  25  ata aat ggg aaa	His Arg Leu Gln Glu Ala Ar 10 15 agg gaa aaa tta aga aga ag Arg Glu Lys Leu Arg Arg Ar	1 ga cag 107 rg Gln ga gaa 155 rg Glu aa aca 203

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<211> 605

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<222> 385..396

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att gag ctg gaa cct ggg ctg agc tcc agt gct gcc tgt aat ggg aag  Ile Glu Leu Glu Pro Gly Leu Ser Ser Ala Ala Cys Asn Gly Lys -15 -10 -5 1	153
gag atg tca cca acc agg caa ctc cgg agg tgc cct gga agt cat tgc Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro Gly Ser His Cys 5 10 15	201
ctg aca ata act gat gtt ccc gtc act gtt tat gca aca acg aga aag Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala Thr Thr Arg Lys 20 25 30	249
cca cct gca caa agc agc aag gaa atg cat cct aaa tagcaccatt Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys 35 40 45	295
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Val Leu Cys Val Leu Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys -10 -5 1 5	
atg agg atg cag aga atc aag gtc tgt gag aag cga ccc agc ata gat	147
Met Arg Met Gln Arg Ile Lys Val Cys Glu Lys Arg Pro Ser Ile Asp 10 15 20	
cta tgc atc cac cac tgt tca tgt ttc caa aag tgt gaa aca aat aag	195
Leu Cys Ile His His Cys Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys 25 30 35	
ata tgc tgt tca gcc ttc tgt ggg aac att tgt atg agc atc cta	240
Ile Cys Cys Ser Ala Phe Cys Gly Asn Ile Cys Met Ser Ile Leu 40 45 50	

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aag ctg ttt gat gcc ccc ttg tcc atc agc aag aga gag cag ctg gaa Lys Leu Phe Asp Ala Pro Leu Ser Ile Ser Lys Arg Glu Gln Leu Glu 10 15 20	160
cag cag gtc cca gag aac tac ttc tat gtg cca gac ctg ggc cag gtg Gln Gln Val Pro Glu Asn Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val 25 30 35 40	208
cct gag att gat gtt cca tcc tac ctg cct gac ctg ccc ggc att gcc Pro Glu Ile Asp Val Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala 45 50 55	256
aac gac ctc atg tac att gcc gac ctg ggc ccc ggc att gcc ccc tct Asn Asp Leu Met Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser 60 65 70	304
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Leu Arg Tyr Phe Glu Phe Ser Thr Phe Leu Leu Ser Leu Ser Leu Ile

-10

-15

-20

	ac tgc Yr Cys														316
cta g	gag cac Slu His			_	-						-				361
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(213/	1101110 1	sapre	113												
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-2215	. sia n	~~+4	•												
	• sig_po		.е												
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	seq M	LFSLS	LLSN	ILNQ/	'IG										
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		accgc	cctt	t gg	gttco	cgaç				Phe S					52
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ctc t Leu S -	gttgc accer asn	ctt Leu caa	aac Asn tca	caa Gln gct	atc Ile 1 cag	ggc Gly ctg	agc Ser	agc Ser att	cac His 5 tac	ctc Leu	Ser I -10 gac Asp atg	eu s cgc Arg tct	cca Pro tca	cac His 10 caa	
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ctc t Leu S att c Ile P caa c Gln L	gettge accept get get get get get get get get get ge	ctt Leu caa Gln cag Gln 30	aac Asn tca Ser 15 cag Gln	caa Gln gct Ala cct Pro	atc Ile 1 cag Gln tcg Ser	ggc Gly ctg Leu gct Ala cta Leu	agc Ser ttt Phe aac Asn 35	agc Ser att Ile 20 aaa Lys	cac His tac Tyr aaa Lys acg	ctc Leu caa Gln gca Ala	Ger I -10 gac Asp atg Met gga Gly cat His	cgc Arg tct Ser aaa Lys 40 ctg	cca Pro tca Ser 25 atc Ile	cac His 10 caa Gln cac His	100 148 196
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ctc t Leu S att c Clie P caa c Gln L aac a Asn T cct t Pro P 75 cgcag agaaa	gettge acceptance of the cag	ctt Leu caa Gln cag Gln 30 ttc Phe caa Gln gct Ala gcagg agccg	aac Asn tca Ser 15 cag Gln gcc Ala att Ile tgc Cys	caa Gln gct Ala cct Pro aac Asn ctt Leu tgaa	atc Ile 1 cag Gln tcg Ser caa Gln cct Pro 65 accc	ggc Gly ctg Leu gct Ala cta Leu 50 ggc Gly	agc Ser ttt Phe aac Asn 35 aat Asn cgt Arg	agc Ser att Ile 20 aaa Lys cca Pro Gln atct	cac His 5 tac Tyr aaa Lys acg Thr tcc ser	ctc Leu caa Gln gca Ala caa Gln ggc Gly 70 aagaa gtcg	Ser I -10 gac Asp atg Met gga Gly cat His 55 agc Ser aggac gatte	cgc Arg tct Ser aaa Lys 40 ctg Leu ctc Leu gct agct	cca Pro tca Ser 25 atc Ile gca Ala acc Thr gctto	cac His 10 caa Gln cac His aaa Lys tca Ser etct egggaga	100 148 196 244 292 347 407 467 527
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ctc ts scale of the case of th	cc aac Ser Asn Sct ggc Pro Gly Sta cag Seu Gln Scc ccc Thr Pro 45 Stt cag Phe Gln Sche Leu Sccgga atcaca aataga	ctt Leu caa Gln cag Gln 30 ttc Phe caa Gln gct Ala gagacaa gatcaa gattgga	aac Asn tca Ser 15 cag Gln gcc Ala att Ile tgc Cys tccc gttt cataatcat gaatt	caa Gln gct Ala cct Pro aac Asn ctt Leu tgaa ct tt	atc Ile 1 cag Gln tcg Ser caa Gln cct Pro 65 accctt agagg	ggc Gly ctg Leu gct Ala cta Leu 50 ggc Gly caa a gattte gaagt ctct ctgaagt ctct ctgaact gaact	agc Ser ttte aac Asn agt agg agg agg agg agg agg agg agg agg	agc Ser att Ile 20 aaa Lys cca Pro Gln atct gatta	cac His 5 tac Tyr aaa Lys acg Thr tcc cagaggaata aggaatagaatg	ctc Leu caa Gln gca Ala caa Gln ggc gly 70 aagaa agaa agaa agaa agaa agaa agaa	Ser I -10 gac Asp atg Met gga Gly cat His ser aggac gattt tagt	cgc Arg cgc Arg tct Ser aaa Lys ctc Leu ctc Leu gct Gag agt Ga	Ser I CCA Pro tca Ser 25 atc Ile gca Ala acc Thr gcttca gattttt gattttt gattaat caata	cac His 10 caa Gln cac His aaa Lys tca Ser ctct cgggaaa gacaggattaaga	100 148 196 244 292 347 407 467 527 587 647 707 767

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Val	Glu	Asp	Phe	Ile	Lys	Ile	Leu	Arg	Glu	Val	Asp	Lys	Ala		Ala	
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cgc gac tgg ctg ctg cgc gag gat gtt tta gaa gaa tgt atg tct Arg Asp Trp Leu Leu Arg Arg Glu Asp Val Leu Glu Glu Cys Met Ser 30 35 40	148
ctt ccc aag cta tct tct tat tct gga tgg gtg gta gag cac gtc cta Leu Pro Lys Leu Ser Ser Tyr Ser Gly Trp Val Val Glu His Val Leu 45 50 55	196
ccc cat atg cag gag aac caa cct ctg tct gag act tcg cca tcc tct Pro His Met Gln Glu Asn Gln Pro Leu Ser Glu Thr Ser Pro Ser Ser 60 65 70	244
acg tca gct tca gcc cta gat caa ccc tca ttt gtt ccc aaa tct cct Thr Ser Ala Ser Ala Leu Asp Gln Pro Ser Phe Val Pro Lys Ser Pro 75 80 85	292
gac gca agc tct gcc ttt tcc cca gcc tcc cct gca aca cca aat gga Asp Ala Ser Ser Ala Phe Ser Pro Ala Ser Pro Ala Thr Pro Asn Gly 90 95 100 105	340
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aat tca aga att atg act cat cgg tca gca gaa aag tgaggatacc Asn Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys 35 40	141
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			130					135					140			622
gga	att	tat	tac	tac	ctg	atg	cag	CCC	agc	ctt	caa	gtg	agc	caa	999	633
GIÀ	IIe		Tyr	Tyr	ьеи	Met	150	PIO	ser	Dea	GIII	155	Ser	GIII	GIY	
		145		++-	ata	220		agt	ata	gac	tac		tgc	cag	cta	681
Lvc	Leu	Uic	Sor	LLG	Val	Lvs	Pro	Ser	Val	Asp	Tvr	Val	Cys	Gln	Leu	•••
Lys	160	1113	001	בים	, m	165					170		-3-			
aaa		cct	tct	qqc	aat	tac	cct	cca	tgt	ata	ggt	gat	aat	cga	gat	729
Lys	Phe	Pro	Ser	Gly	Asn	Tyr	Pro	Pro	Cys	Ile	Gly	Asp	Asn	Arg	Asp	
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atc	cag	gcc	tat	aag	gta	ttc	aga	gag	gaa	aag	Tac	CEC	tgt	gat Nen	gee ala	623
TIE	GIN	ATA	1yr 210	гÀè	val	Pne	Arg	215	Giu	пуs	TYL	пеп	Cys 220	Asp	ALG	
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	Tyr	Asn	Leu	Thr		Asp	Met	Lys	Tyr		Tyr	Arg	Ala	Cys	ьуs 270	
255		~			260	~~~	+=+	~~~	~~~	265	~~	tac	aga	202		1017
Dhe	gct ala	Glu	Trn	Cve	T.e.	Glu	Tvr	Glv	Glu	His	Glv	Cvs	Arg	Thr	Pro	
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Asp	Thr	Pro	Phe	Ser	Leu	Phe	Glu	Gly	Met	Ala	Gly	Thr	Ile	Tyr	Phe	
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aca aaa aaa aaa aaa aaa aa aa aa Thr Lys Lys Lys Lys Lys Sys Lys Sys Lys Lys Sys Lys Lys Sys Lys Lys Sys Lys Lys Lys Lys Lys Lys Lys Lys Lys L	gaa aaa cac aca cac aca cac aca cat ata cac aca cac aca cga aaa Glu Lys His Thr His Thr His Ile His Thr His Thr Arg Lys	401
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Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser Asp Leu Lys Arg Ile Asn

15 tcc tca tct cta agg ctt acc aga agc tct gat ttg aag aga ata aat

10

101

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Tyr	Asn	Arg	Val	Pro	Leu	His	Lys	Pro	Thr	Asp	Trp	Gln	Lys	Lys	Ile	
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ctc	ata	tgg	tca	ggt	cgc	ttc	aaa	aag	gaa	gat	gaa	atc	cca	gag	act	293
Leu	Ile	Trp	Ser	Gly	Arg	Phe	Lys	Lys	Glu	Asp	Glu	Ile	Pro	Glu	Thr	
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gtc	tcg	ttg	gag	atg	ctt	gat	gct	gca	aag	aac	aag	atg	cga	gtg	aag	341
Val	Ser	Leu	Glu	Met	Leu	Asp	Ala	Ala	Lys	Asn	Lys	Met	Arg	vaı	гÀг	
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agc	agc	tat	cta	atg	att	gcc	ctg	acg	gtg	gta	gga	tgc	atc	Dho	Met	369
Ser	Ser		Leu	Met	Ile	Ala		Thr	vaı	vaı	GIĀ	115	TTE	PILE	Mec	
		105					110				~~~		++=	202	200	437
gtt	att	gag	'āāc	aag	aag	gct	gcc	Caa	aya	Tic	gay	Thr	Lua	Thr	Ser	45,
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ttg	aac	tta	gaa	aag	aaa	get	ZGC	Lou	Lvc	Glu	Glu	λla	Ala	Met	Lvs	•••
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135					140		- -	~+~+	ta a		s+++	t da	aaati	ccaq		537
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Ala	гуs	Thr	GIU		aa t	~+	+222	2 20	rata.	taat	ato	agga	tcc .	attt	cataaa	597
gaa	ttat	gtt	ataa	cgtg	-~ -	grac	taaa tttc	a ay	attt	ctac	cat	адза адаа	ota (gaaa	taaatt	657
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Cys Ala Tyr Lys Lys Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu 80 85 90	
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			cga													1309
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Ile	Val	Ser	Lys 395		Leu	Thr	Asn	Ser		Phe	Phe	Leu	Phe 405	Asp	Phe	
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	425		Gln		-	430		_								
															cctggc	1518
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gcc Ala	tcg Ser	Leu	gag	atc Ile	gag Glu	tac Tyr	caa Gln 40	gtt	tta Leu	gat Asp	gga Gly	gca Ala 45	gga Gly	tta Leu	gat Asp	244
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caa Gln	50 aga Arg	aaa Lys	tca Ser	gat Asp	gga Gly	55 gtt Val	cac His	act Thr	gta Val	Glu	act	gaa Glu	gtt Val	ggt Gly	gat Asp 80	340
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att Ile	ttc Phe	ttt Phe	gaa Glu	85 tta Leu	atc Ile	ctg Leu	gat Asp	Asn	90 atg Met	gga Gly	gaa Glu	cag Gln	gca Ala	95 caa Gln	gaa Glu	436
caa Gln	gaa Glu	gat Asp	100 tgg Trp	aag Lys	aaa Lys	tat Tyr	Ile	Thr	ggc Gly	aca Thr	gat Asp	Ile	110 ttg Leu	gat Asp	atg Met	484
aaa Lys	ctg Leu	115 gaa Glu	gac Asp	atc Ile	ctg Leu	gaa Glu	120 tcc Ser	atc	agc Ser	agc Ser	Ile	125 aag Lys	tcc Ser	aga Arg	cta Leu	532
agc	130 aaa	agt	aaa	cac	ata	135 caa	att	ctg	ctt	aga	140 gca	ttt	gaa Glu	gct	cgt Arg	580
145 gat	cga	aac	ata	caa	150 gaa	agc	aac	ttt	gat	155 aga	gtc	aat	ttc Phe	tgg	tct	628
ato	att	aat	tta	165 ata	atc	atq	gtg	gtg	170 gtg	tca	gcc	att	caa Gln	175 gtt	tat	676
ato	ctq	aaq	180 agt Ser	ctg	ttt	gaa	gat	185 aag	agg	aaa	agt	aga	190 act			718
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<211> 787

<212> DNA

<213> Homo sapiens

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<221> sig_peptide <222> 26..88

<223> Von Heijne matrix

score 4.4 seq AVASSFFCASLFS/AV

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gtg	gct	tcc	agt	ttc	ttt	tgt	gca	tct	ctc	ttc	tca	gct	gtg	cac	aag	100
Val	Ala	Ser	Ser	Phe	Phe	Cys	Ala	Ser	Leu	Phe	Ser	Ala	Val	His	Lys	
		-10					- 5					1				
ata	gaa	gag.	gga	cat	att	999	gta	tat	tac	aga	ggc	ggt	gcc	ctg	ctg	148
Ile	Glu	Glu	Gly	His	Ile	Gly	Val	Tyr	Tyr	Arg	Gly	Gly	Ala	Leu	Leu	
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act	tcg	acc	agc	ggc	cct	ggt	ttc	cat	ctc	atg	ctc	cct	ttc	atc	aca	196
Thr	Ser	Thr	Ser	Gly	Pro	Gly	Phe	His	Leu	Met	Leu	Pro	Phe	Ile	Thr	
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tca	tat	aag	tct	gtg	cag	acc	aca	ctc	cag	aca	gat	gag	gtg	aag	aat	244
Ser	Tyr	Lys	Ser	Val	Gln	Thr	Thr	Leu	Gln	Thr	Asp	Glu	Val	Lys	Asn	
			40					45					50			
gta	cct	tgt	999	act	agt	ggt	ggt	gtg	atg	atc	tac	ttt	gac	aga	att	292
Val	Pro	Cys	Gly	Thr	Ser	Gly	Gly	Val	Met	Ile	Tyr	Phe	Asp	Arg	Ile	
		55					60					65				
gaa	gtg	gtg	aac	ttc	ctg	gtc	ccg	aac	gca	gtg	cat	gat	ata	gtg	aag	340
Glu	Val	Val	Asn	Phe	Leu	Val	Pro	Asn	Ala	Val	His	Asp	Ile	Val	Lys	
	70					75					80					
aac	tat	act	gct	gac	tat	gac	aag	gcc	ctc	atc	ttc	aac	aag	atc	cac	388
Asn	Tyr	Thr	Āla	Asp	Tyr	Asp	Lys	Ala	Leu	Ile	Phe	Asn	Lys	Ile	His	
85					90					95					100	
cac	gaa	ctg	aac	cag	ttc	tgc	agt	gtg	cac	acg	ctt	caa	gag	gtc	tac	436
His	Glu	Leu	Asn	Gln	Phe	Cys	Ser	Val	His	Thr	Leu	Gln	Glu	Val	Tyr	
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att	gag	ctg	ttt	gga	ctg	gaa	aat	gat	ttt	tcc	cag	gaa	tct	tca		481
Ile	Glu	Leu	Phe	Gly	Leu	Glu	Asn	Asp	Phe	Ser	Gln	Glu	Ser	Ser		
			120	_				125					130			
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att	actt	tta :	atgt	ttct	gc a	gtag	aaaa	t ga	atct	aaat	tca	tttt	ata	gggt	ttgtag	661
tct	ttta	tct	gttt	tgga [.]	tt c	actg	tgct	t tt	aaga	aaaa	gtt	ggta	aat	ttgc	cgttga	721
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<211> 569

<212> DNA

<213> Homo sapiens

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<222> 26..562

<221> sig_peptide <222> 26..187

<223> Von Heijne matrix score 4.1

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					aaa Lys -40											100	
gga					atg Met											148	
gcg Ala	gtg Val	gtt Val	gcg Ala -10	gcc Ala	gcg Ala	gcc Ala	agg Arg	acc Thr -5	gga Gly	tcc Ser	gaa Glu	gcc Ala	agg Arg 1	gtc Val	tcc Ser	196	
					acc Thr											244	
					999 Gly 25											292	
aag Lys	gag Glu	aag Lys	ctg Leu	ctg Leu 40	gca Ala	gaa Glu	gct Ala	gga Gly	atg Met 45	cct Pro	tct Ser	cca Pro	gaa Glu	tgg Trp 50	acc Thr	340	
					act Thr											388	
					gtt Val											436	
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gaa	_				ggt Gly	_					gtag					569	

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<222> 4..810

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<222> 4..279

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<222> 881..893

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			-90					-85					-80		cat	96
ctg Leu	ctt Leu	gaa Glu -75	gag Glu	Leu	ccc Pro	Leu	Pro	gac Asp	Gln	Gln	Pro	Cys -65	Ile	Glu	Pro	70
cca Pro	Pro	tcc	tcc Ser	atc Ile	atg Met	Tyr	cag Gln	gct Ala	aac Asn	ttt Phe	Asp	aca Thr	aac Asn	ttt Phe	gag Glu	144
qac	-60 agg	aat	gca	ttt	gtc	-55 acg	ggc	att	gca	agg	-50 tac	att	gag	cag	gct	192
Asp -45	Arg	Asn	Ala	Phe	Val -40	Thr	Gly	Ile	Ala	Arg	Tyr	Ile	Glu	Gln	Ala -30	
	atc	cac	tcc	agc	atg	aat	gag	atg	ctg	gag	gaa	gga	cat	gag	tat	240
Thr	, Val	His	Ser	Ser -25	Met	Asn	Glu	Met	Leu -20	Glu	Glu	Gly	His	Glu -15	Tyr	
gcg	gtc	atg	ctg	tac	acc	tgg	cgc	agc	tgt	tcc	cgg	gcc	att	CCC	cag	288
			-10		Thr			-5					1			
gtg	aaa	tgc	aac	gag	cag	CCC	aac	cga	gta	gag	atc	tat	gag	aag	aca	336
	5				Gln	10					15			•		
gta	gag	gtg	ctg	gag	ccg	gag	gtc	acc	aag	ctc	atg	aag	ttc	atg	tat	384
20					Pro 25					30					35 -	
ttt	cag	cgc	aag	gcc	atc	gag	cgg	ttc	tgc	agc	gag	gtg	aag	cgg	ctg	432
				40	Ile				45					50		
tgc	cat	gcc	gag	cgc	agg	aag	gac	ttt	gtc	tct	gag	gcc	tac	ctc	ctg	480
			55		Arg			60					65			
acc	ctt	ggc	aag	ttc	atc	aac	atg	ttt	gct	gtc	ctg	gat	gag	cta	aag	528
		70			Ile		75					80				F.7.6
aac	atg	aag	tgc	agc	gtc	aag	aat	gac	cac	tcc	gcc	tac	aag	agg	gca	576
	85				Val	90					95					
gca	cag	ttc	ctg	cgg	aag	atg	gca	gat	CCC	cag	tct	atc	cag	gag	tcg	624
		Phe	Leu	Arg	Lys	Met	Ala	Asp	Pro	110	ser	TIE	GIN	GIU	115	
100		c++	tcc	ata	105 ttc	cta	acc	aac	cac		aaa	atc	acc	caq		672
Gln	Asn	Leu	Ser	Met 120	Phe	Leu	Ala	Asn	His	Asn	Arg	Ile	Thr	Gln 130	Cys	• •
ctc	cac	cao	caa			ata	atc	cca			qaq	qaq	ctg		gct	720
Leu	His	Gln	Gln 135	Leu	Glu	Val	Ile	Pro	Gly	Tyr	Glu	Glu	Leu 145	Leu	Ala	
gac	att	gto			tgt	gtg	gat	tac	tac	gag	aac	aag	atg	tac	ctg	768
Asp	Ile	Val 150	Asn	Ile	Cys	Val	Asp	Tyr	Туг	Glu	Asn	Lys 160	Met	Туг	Leu	
act	ccc	agt	gag	aaa	cat	atg	cto	cto	aag	gta	aaa	cto	ccc	:		810
Thr	Pro	Ser	Glu	Lys	His	Met	Lev	Leu	Lys	Val	Lys	Leu	Pro	•		
	165				•	170					175					070
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score 3.5

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agg aga cag agg ctg gcc gag ctg cag gcc aaa cac ggg gat cct ggt Arg Arg Gln Arg Leu Ala Glu Leu Gln Ala Lys His Gly Asp Pro Gly	99
gat gcg gcc caa cag gaa gca aag cac agg gaa gca gaa atg aga aac Asp Ala Ala Gln Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg Asn	147
-25 -20 -15 agt atc tta gcc caa gtt ctg gat cag tcg gcc cgg gcc agg tta agt Ser Ile Leu Ala Gln Val Leu Asp Gln Ser Ala Arg Ala Arg Leu Ser	195
-10 -5 1 aac tta gca ctt gta aag cct gaa aaa act aaa gca gta gag aat tac Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr	243
5 10 15 Ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca gaa Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu	291
20 25 30 35 caa ggt tta ata gaa atc ctt aaa aaa gta agc caa caa aca gaa aag Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Lys	339
40 45 50 aca aca aca gtg aaa ttc aac aga aga aaa gta atg gac tct gat gaa Thr Thr Thr Val Lys Phe Asn Arg Arg Lys Val Met Asp Ser Asp Glu	387
55 60 65 gat gac gat tat tgaactacaa gtgctcacag actagaactt aacggaacaa Asp Asp Asp Tyr	439
70 gtctaggaca g	450
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ccg ccg cca ccc ctg tat acc cgg cac cgc atg ctc ggt cca gag tcc Pro Pro Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser -5 1 5	99
gtc ccg ccc cca aaa cga tcc cgc agc aaa ctc atg gca ccg ccc cga Val Pro Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg 10 15 20 25	147

·	•															
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gca Ala	ctg Leu	ctt Leu	Arg	30 ctc Leu	ctg Leu	ccg Pro	gag Glu	Tyr	cgg	gat Asp	gca Ala	gag Glu	att Ile 55	gtg	cgg Arg	243
acc Thr	cgg Arg	Asp	45 ccc Pro	gaa Glu	aaa Lys	ctc Leu	Ala	50 tcc Ser	tgt Cys	gac Asp	atc Ile	gtg Val	gtg	gac Asp	gtg Val	291
Gly aaa	Gly	60 gag Glu	tac Tyr	gac Asp	cct Pro	Arg	65 aga Arg	cac His	cga Arg	tat Tyr	Asp	70 cat His	cac His	cag Gln	agg Arg	339
Ser	75 ttc Phe	aca Thr	gag Glu	acc Thr	Met	80 agc Ser	tcc Ser	ctg Leu	tcc Ser	Pro	85 999 61y	agg Arg	ccg Pro	tgg Trp	cag Gln 105	387
90 acc Thr	aag Lys	ctg Leu	agc Ser	Ser	95 gcg Ala	gga Gly	ctc Leu	atc Ile	Tyr	100 ctg Leu	cac His	ttc Phe	ggg ggg	cac His 120	aag	435
ctg Leu	ctg Leu	gcc Ala	Gln	110 ttg Leu	ctg Leu	ggc Gly	act Thr	Ser	115 gaa Glu	gag Glu	gac Asp	agc Ser	atg Met 135	gtg	ggc Gly	483
acc Thr	ctc Leu	Tyr	125 gac Asp	aag Lys	atg Met	tat Tyr	gag Glu 145	130 aac Asn	ttt Phe	gtg Val	gag Glu	gag Glu 150	gtg	gat Asp	gct Ala	531
gtg Val	Asp	140 aat Asn	Gly 999	atc Ile	tcc Ser	cag Gln 160	tgg	gca Ala	gag Glu	ggg ggg	gag Glu 165	cct Pro	cga Arg	tat Tyr	gca Ala	579
Leu	155 acc Thr	act Thr	acc Thr	ctg Leu	Ser	gca	cga Arg	gtt Val	gct Ala	cga Arg 180	ctt Leu	aat Asn	cct Pro	acc Thr	tgg Trp 185	627
170 aac Asn	cac His	ccc Pro	gac Asp	Gln	Asp	act Thr	gag Glu	gca Ala	999 Gly 195	ttc Phe	aag	cgt Arg	gca Ala	atg Met 200	gat Asp	675
ctg Leu	gtt Val	caa Gln	Glu	Glu	ttt	ctg Leu	cag Gln	aga Arg 210	tta Leu	gat	ttc Phe	tac Tyr	caa Gln 215	cac His	agc	723
tgg Trp	ctg Leu	Pro	Ala	cqq	gcc Ala	ttg Leu	gtg Val	gaa Glu	gag	gcc Ala	ctt Leu	gcc Ala 230	cag Gln	cga	ttc Phe	771
cag Gln	Val	Asp	cca	agt Ser	gga Gly	Glu	att	gtg	gaa Glu	ctg Lev	gcg Ala 245	aaa Lys	ggt	gca Ala	tgt Cys	819
Pro	Trp	aag	gag Glu	cat His	Leu	Tyr	cac	ctg Leu	gaa Glu	tct Ser 260	Gly	g ctg / Leu	tcc	cct Pro	cca Pro 265	867
250 gtg Val	gco	ato Ile	tto Phe	ttt Phe	val	ato	tac Tyr	act Thr	gac Asp	caç Glr	gct	gga Gly	cag Gln	tgg Trp 280	cga Arg	915
ata Ile	cag Glr	tgt Cys	gtg Val	ccc Pro	aag	gag Glu	cco Pro	cac His	tca Ser	tto	caa Glr	a ago n Ser	cgg Arg	ctg Lev	ccc Pro	963
cto Lev	cca Pro	gag Glu	g cca	tgg	g cgg	ggt Gly	ctt Lev	cgg Arg	gac	gag Glu	g gco n Ala	ctg Leu 310	gac Asp	cag	gtc Val	1011
agt Ser	gg9 Gl ₃	g ato	cct	ggc Gly	tgo Cys	ato 320	tto Phe	gto	cat His	gca Ala	ago Ser 325	ggc Gly	tto	att Ile	ggc Gly	1059
ggt Gl ₃ 330	cac His	c cg	aco Thi	cga Arg	a gag g Glu 335	g ggt 1 Gly	gcc	ttg a Lev	g ago	ato Met	g gcd : Ala	cgt	gco g Ala	aco Thi	ttg Leu 345	1107
gc	cag				cto	cca		a ato n Ile		tag		aata	aaac	ctto		1157

355

350 tctcaaaaaa aaaaaa

1173

686

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155

150

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Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu Arg Gln Arg Arg -55 -50 -45	
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Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln Cys Trp Trp Arg	
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Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln Ala Leu Leu Arg 10 15 20	
qtc tac qtc atc cag gag cag gcg acg gtc aag ctc cag tcc tgc atc	343
Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu Gln Ser Cys Ile	
25	391
Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met Cys Asn Ala Leu 50 55	
the field free card die com and man and and and and and and	139
Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe Gln Thr Asp Gly 60 65 70	
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                                 -25
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 Ser Thr
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	~~+	~~~	1	a > a	ata	cca	2	ctc	ttc	taa	aag		tac	atc	tat	201
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gcc	tct Ser	Dhe	acc	Tac	CCC	Ser	Len	Ser	Δla	Len	Ala	His	Leu	ctg Leu	Gln	***
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Ala 110	Lys	Ser	Glu	Phe	Trp 115	His	Tyr	Ser	Phe	Phe 120	Phe	Leu	Asp	Tyr	Val 125	
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GIY	Val	Ala	Val	Tyr 130	GIn	Pne	GIY	Ser	135	Leu	ALA	HIS	PIIE	Tyr 140	TYL	
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Ile	Phe	Val	Ser	Ser 210	Asp	Pro	Thr	Thr	Asp 215	Asp	Pro	Ala	Leu	Leu 220	Tyr	
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ccc atg ttg ttt tgt gaa g Pro Met Leu Phe Cys Glu F 10		
aag tot cac aag aca tgg g Lys Ser His Lys Thr Trp G 25		
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Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys

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-10 -5 1 5 att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg	153
Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met 10 15 20	201
tgc ttt ttt gat tct gag gat cct gca aat tcc ctt cgt gga gga gag Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Glu 25 30 35	201
cct aac ttc ctg cct gtg act gag gag gct gac att cgt gag gat gac Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile Arg Glu Asp Asp 40 45 50	249
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gac ttg ttg ctg ggg atc tgc tat ctg atg ccc ctc aat act tct att Asp Leu Leu Cly Ile Cys Tyr Leu Met Pro Leu Asn Thr Ser Ile 90 95 100	393
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ttc ccc aac gaa ttt att gtt gag acc aag atc tgt caa gag Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys Gln Glu 185 190 195	675
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90

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395

575

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105 ccaaggggca agagctttca tgtgcaagag gcaaggaaac tgattatctt gagtaaatgc cageetttgg getaagtact taccacagag tgaatettca aaaaatgate ataattattt

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100

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a atg tct tca ggc cgg ctg cgg tgg ctc atg cct gta atc cca gca ctt Met Ser Ser Gly Arg Leu Arg Trp Leu Met Pro Val Ile Pro Ala Leu -15 -10 -5	469
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	217
Met Met Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys 1 5 10	
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Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile 35 40 45	
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Ala His Ile Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val 50 60	
50 55 60	

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                            Met Phe Ala Pro Ala Val Met Arg Ala
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                                                         -25
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Phe Arg Lys Asn Lys Thr Leu Gly Tyr Gly Val Pro Met Leu Leu Leu
            -20
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Ile Val Gly Sly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
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Asp Ala Val Lys Ser Lys Met Asp Pro Glu Leu Glu Lys Lys Leu Lys
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Glu Asn Lys Ile Ser Leu Glu Ser Glu Tyr Glu Lys Ile Lys Asp Ser
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Lys Phe Asp Asp Trp Lys Asn Ile Arg Gly Pro Arg Pro Trp Glu Asp
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                                                                      400
cct gac ctc ctc caa gga aga aat cca gaa agc ctt aag act aag aca
Pro Asp Leu Leu Gln Gly Arg Asn Pro Glu Ser Leu Lys Thr Lys Thr
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\22.		core		· iliai	-11^											
		eq LV		LILI	CILT,	/IW				•						
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			-30			-	_	-25	•				-20	Xaa		
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V10	Aaa	-15	Deu	пеа	vai	PHE	-10	FILE	ьец	Leu	116	-5	TIII	116	Deu	
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	65					70					75					
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aac tat acg gat Asn Tyr Thr Asp 80	ttt gag gac t	tca ccc tac ttc aa Ser Pro Tyr Phe Ly 85	rs Met His Lys Pro 90	
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PCT/IB98/02122 -

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Cys Gly Ser His Leu Trp Arg Glu Ser His His
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·Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ilé Glu Tyr Gln Val
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Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
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Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
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Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
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Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
                                      100
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Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
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Val Phe
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-119-

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-15

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-10

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150 155 Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu 170 165 Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro 180 185 190 Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln 205 195 200 Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys 215 Ser Thr Phe Ile 225

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Arg Gly Ser Leu Glu Pro Gly Arg Leu Arg Leu Gln

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 -50

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 -40
 -35

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Leu Ser Glu Lys Gly Asp Ser Gln Pro Ser Ala Ser 45 50 55

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WO 99/31236 -126- PCT/IB98/02122 -

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<213> Homo sapiens

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<210> 170 <211> 252 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1

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-65 -60 -55

Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 -30 -35 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 120 115 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 135 130 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys

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85 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 105 100 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 115 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 135 130 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 165 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 180 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 200 195 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 215 210 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 230 225 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 240 245 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 260 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser 275

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<222> -68..-1

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Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 135 130 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 160 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 180 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 200 195 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 215 210 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Ser Lys Ala Thr Gln 230 225 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 245 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 265 260 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 280 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 295 290 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 305 Glu Gly Thr Ser Ala Ser 320

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Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His

80 85 90
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210> 10

<211> 59

<212> PRT

<213> Homo sapiens

<400> 180

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

10 15
Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg
20 25 30
Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu
35
Thr Pro Arg Lys Arg Glu Gly Lys Lys Lys Lys
50 55

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<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<210> 181

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To Solve The Leu Leu Gly Leu Ala Phe Cys 90 95 100

Leu His Pro Trp Ala 105

<210> 183 <211> 80 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -35..-1 <400> 183 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly -35 -30 -25 -20 Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ser Ala Ala -5 -10 -15 Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro 5 10 Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala

Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys

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<222> -21..-1

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<210> 185
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Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser

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<210> 186
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Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                       10
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
                   25
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
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70

<220> <221> SIGNAL

<222> -42..-1 <400> 189

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-5

Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg 60

Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys

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155 160 165

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<210> 191 <211> 379 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -37..-1

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65 Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln 80 Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile 100 Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala 115 120 Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln 135 130 Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly 150 145 Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val 165 160 Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys 180 175 Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr 195 Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr 210 215 Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser 230 225 Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala 245 240 Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu 260 255 Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp 275 280 Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu 295 290 Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro 310 305 Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met 325 320 Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser 335

<210> 192 <211> 112 <212> PRT <213> Homo sapiens

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<211> 43 <212> PRT <213> Homo sapiens Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser 10 Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn 25 Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys 35 <210> 194 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL . <222> -16..-1 <400> 194 Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala -10 Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu 5 10 Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu 25 20 Pro Asn Phe 35 <210> 195 <211> 244 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 195 Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala -10 Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile 20 25 Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys 40 Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp 55 Val Thr Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly 70 Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala

85

100

Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

90

120 115 Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro 130 135 Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln 150 Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp 165 170 Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro 185 180 His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val 195 200 Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly 215 210 Arg Thr Ala Trp 225

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<222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -30 -25 -20 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val ~5 -10 -15 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln 1 5 10 Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 25 20 Ala Gly Pro Leu Ala Val Ala Ala Val Leu Tyr His Lys Met Asn Asn 40 35 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 75

Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 90 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 115 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 150 155 145 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 185 180 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200

Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala
210 215 220

Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly

Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr
240

Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys Lys
255

Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr
275

Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe
290

Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu
305

Leu Ala Cys Lys
267

270

Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe
290

300

Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu
305

<210> 197 <211> 30 <212> PRT <213> Homo sapiens

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<213> Homo sapiens
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<222> -48..-1

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<210> 199 <211> 54 <212> PRT <213> Homo sapiens

 Pro
 Arg
 Trp
 His
 Arg
 Leu
 Pro
 Pro
 Gln
 Ser
 Leu
 Gln
 His
 Gln
 Tyr

 Cys
 Gln
 Arg
 Arg
 Trp
 Pro
 Asp
 Arg
 Arg
 Cys
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 Gln
 Ser
 His
 Thr
 Gln

 Ser
 Ser
 Gly
 His
 Leu
 Pro
 40
 45
 45

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<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

125

 4400> 201

 Met Ser Met Ala Val Glu Thr Phe Gly Phe Phe Met Ala Thr Val Gly -25
 -20
 -15
 -10

 Leu Leu Met Leu Gly Val Thr Leu Pro Asn Ser Tyr Trp Arg Val Ser -5
 1
 5

 Thr Val His Gly Asn Val Ile Thr Thr Asn Thr Ile Phe Glu Asn Leu 10
 15
 20

 Trp Phe Ser Cys Ala Thr Asp Ser Leu Gly Val Tyr Asn Cys Trp Glu 25
 30
 35

 Phe Pro Ser Met Leu Ala Leu Ser Gly Tyr Ile Gln Ala Cys Arg Ala 40
 45
 50

Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Gly Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg 110 115 Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro 130 125 Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly 145 140 Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala 160 165 155 Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val 180 175 Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg 190 Asn Ala Tyr Val

<210> 202 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

<210> 203
<211> 146
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 203

Met Met Trp Gln Lys Tyr Ala Gly Ser Arg Arg Ser Met Pro Leu Gly
-30 -25 -20

Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly Gly Phe Ala Ile
-15 -10 -5 1

Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Ala Leu Tyr Tyr Lys
5 10 15

Leu Ala Val Glu Gln Leu Gln Ser His Pro Glu Ala Gln Glu Ala Leu
20 25 30

<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<210> 205 <211> 40 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

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10 Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser 25 Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro 40 Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr 60 55 Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu 75 70 Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys 90 85 Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val 110 100 105 Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg 125 120 His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys 135 Glu Glu Ala Ala Met Lys Ala Lys Thr Glu 150

<210> 207 <211> 101 <212> PRT

<213> Homo sapiens

<400> 207 Met Val Cys Glu Lys Cys Glu Lys Lys Leu Gly Thr Val Ile Thr Pro 10 Asp Thr Trp Lys Asp Gly Ala Arg Asn Thr Thr Glu Ser Gly Gly Arg 30 20 Lys Leu Asn Lys Asn Lys Ala Leu Thr Ser Lys Lys Ala Arg Phe Asp 45 40 Pro Tyr Gly Lys Asn Lys Phe Ser Thr Cys Arg Ile Cys Lys Ser Ser 55 Val His Gln Pro Gly Ser His Tyr Cys Gln Gly Cys Ala Tyr Lys Lys 75 70 Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr 90 85 Lys Gln Thr Ser Val 100

<210> 208 <211> 456 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -22..-1

<400> 208 Met Phe Glu Glu Pro Glu Trp Ala Glu Ala Ala Pro Val Ala Ala Gly -15 -10 -20 Leu Gly Pro Val Ile Ser Arg Pro Pro Pro Ala Ala Ser Ser Gln Asn 1 Lys Gly Ser Lys Arg Arg Gln Leu Leu Ala Thr Leu Arg Ala Leu Glu 20 Ala Ala Ser Leu Ser Gln His Pro Pro Ser Leu Cys Ile Ser Asp Ser

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35
Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
                                             55
                          50
Phe Ala Ser Ala Glu Val Gly Lys Lys Lys Lys Lys Cys
                      65
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
                                      85
                  80
Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
                                  100
               95
Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
                                                 120
                              115
           110
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
                                           . 135
                          130
       125
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
                                         150
                       145
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
                  160
                                     165
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
                                 180
               175
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
                             195
           190
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
                         210
                                              215
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
                   225
                                          230
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
                  240
                                      245
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
                                  260
               255
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
                               275
           270
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
                                              295
                           290
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
                                          310
                       305
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
                                      325
                   320
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                                   340
               335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
            350
                               355
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
                                              375
                           370
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
                                          390
                       385
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
                                      405
                  400
 Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
           415
                                   420
 Gln Pro Cys Leu Tyr Lys Arg Arg
            430
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<210> 209 <211> 98

<212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -17..-1

<400> 209 Met Pro Ser Ser Phe Phe Leu Leu Leu Gln Phe Phe Leu Arg Ile Asp -10 -5 -15 Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp 10 5 Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser 2.5 20 Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile 35 . 40 Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe 55 60 Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln 70 Val Glu 80

<210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

<400> 210 Met Thr Leu Leu Ser Phe Ala Ala Phe Thr Ala Ala Phe Ser Val Leu -20 -25 Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg Ala Leu Ala Ser Val Phe -5 -10 Asp Pro Leu Cys Val Cys Ser Arg Val Leu Pro Thr Pro Val Cys Thr 10 15 Leu Val Ala Thr Gln Ala Glu Lys Ile Leu Glu Asn Gly Pro Cys Pro 30 25 Thr Lys Glu Ala Ala Gln Leu Val Gly Lys Gly Ser Val Ser Ala Arg 40 45 Asn Ala Ser

<210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1

50 Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr 65 Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn 100 Met Gly Glu Gln Ala Gln Glu Glu Asp Trp Lys Lys Tyr Ile Thr 115 110 Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile 135 130 125 Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu 150 145 Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe 165 160 Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val 180 175 Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys 195 190 Arg Lys Ser Arg Thr 205.

<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -10 -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 15 20 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 35 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val 65 Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 100 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 110 Asn Asp Phe Ser Gln Glu Ser Ser 125 . 130

<210> 213 <211> 179 <212> PRT <213> Home sapiens <220> <221> SIGNAL <222> -54..-1

<400> 213

Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr -45 -50 Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala -30 -35 Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Val Ala Ala Ala Ala -10 -15 Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu 30 Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu 50 Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu 65 Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser 85 80 Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp 100 105 Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met 115 Asn Leu Ile 125

<210> 214 <211> 269 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 214

<222> -92..-1

Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu -85 -90 Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro -70 -65 Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp -50 -55 Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr -40 -35 Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala -20 Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val - 5 Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val 15 Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe 30 Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys 40 45 His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr 60

Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn 70 75 Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala 95 90 Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln 110 105 Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu 120 125 His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp 140 145 Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr 155 160 Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro 170

<210> 215 <211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

<400> 215

Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 -10 -20 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala 1 Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 40 30 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 45 50 55 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu 70 65 Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 85 80 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 95 100 Ser Ala Pro Lys Ser Asn Val

<210> 216 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -38..-1 <400> 216

110

Met Asn Asn Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser
-35
-30
-25

Val Lys Gly His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr
-20
-15

Ala Val Cys Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu -5 1 5 5 10

Phe Asn Pro Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu Val Leu 25

Glu Val Leu

<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1

<400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -50 -45 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Gln Glu Ala -30 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -15 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro 5 Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 20 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn 50 Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr

100 105 Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu 115 . Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu 130 135 Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp 150 145 Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr 170 165 160 Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His 180 175 Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val 200 195 190 Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu 215 210 Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val 230 225 Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp 240 245 Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala 260 255 Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln 275 270 Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro 290 295 Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly 305 310 Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His 325 ... 330 320 Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln 340 335 Arg Ser Tyr Leu Pro Gln Ile Ser 350

<210> 219 <211> 211 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL

<222> -30..-1

<400> 219

Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val -25 -20 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro -10 -5 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 30 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 70 75 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe

His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro 105 110 Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser 120 125 Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly 140 135 Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser Ser His Ser 150 155 Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser 170 175 Arg Gln Leu 180

<210> 220 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
-25 -20 -15

Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
-10 -5 1

Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln

10 15 20

Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu
25 30 35

Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 40 45 50

Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe 55 60 65

Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 70 75 80

Pro Glu Phe His Ile Glu Ile Leu Ser Ile 85 90

<210> 221 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 221

Met Lys Gly Gly Ala Phe Ser Asn Leu Asn Asp Ser Gln Leu Ser Ala
-40 -35 -30

Ser Phe Leu Gln Pro Ser Leu Gln Ala Asn Cys Pro Ala Leu Asp Pro
-25 -20 -15

Ala Val Ser Leu Ser Ala Pro Ala Phe Ala Ser Ala Leu Arg Ser Met -5 -10 Lys Ser Ser Gln Ala Ala Arg Lys Asp Asp Phe Leu Arg Ser Leu Ser 15 10 Asp Gly Asp Ser Gly Thr Ser Glu His Ile Ser Ala Val Val Thr Ser 30 Pro Arg Ile Ser Cys His Gly Ala Ala Ile Pro Thr Ala Arg Ala Leu 45 50 Cys Leu Gly Cys Ser Cys Cys Thr Glu Arg Leu Leu Pro Pro Pro 60 65 Ser Leu Leu Ser Leu Glu Ala Pro Ala Ser Thr 75

-10 Val Ile Gln Glu Pro Gln Leu Ser Leu Gln Pro Glu Pro Val Phe Thr 5 Val Asp Arg Ala Glu Val Pro Pro Leu Phe Trp Lys Pro Tyr Ile Tyr 20 25 Ala Gly Tyr Arg Pro Leu His Gln Thr Trp Arg Phe Tyr Phe Arg Thr 35 · 40 Leu Phe Gln Gln His Asn Glu Ala Val Asn Val Trp Thr His Leu Leu 50 55 Ala Ala Leu Val Leu Leu Arg Leu Ala Leu Phe Val Glu Thr Val 70 Asp Phe Trp Gly Asp Pro His Ala Leu Pro Leu Phe Ile Ile Val Leu 85 Ala Ser Phe Thr Tyr Leu Ser Leu Ser Ala Leu Ala His Leu Leu Gln 100 105 Ala Lys Ser Glu Phe Trp His Tyr Ser Phe Phe Phe Leu Asp Tyr Val 115 120 125 Gly Val Ala Val Tyr Gln Phe Gly Ser Ala Leu Ala His Phe Tyr Tyr 130 135 140 Ala Ile Glu Pro Ala Trp His Ala Gln Val Gln Ala Val Phe Leu Pro 145 150 Met Ala Ala Phe Leu Ala Trp Leu Ser Cys Ile Gly Ser Cys Tyr Asn 165 170 Lys Tyr Ile Gln Lys Pro Gly Leu Leu Gly Arg Thr Cys Gln Glu Val 175 180 185 Pro Ser Val Leu Ala Tyr Ala Leu Asp Ile Ser Pro Val Val His Arg 195 200 Ile Phe Val Ser Ser Asp Pro Thr Thr Asp Asp Pro Ala Leu Leu Tyr 215 210 His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Ala Phe Phe Ser 230 225

Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly 240 245 250
Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala

Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

265

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-10 -15 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp 1 . 10 Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr 35 Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg 50 55 Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 65 70 Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 80 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100 105 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 150 145 His Leu Leu Ala Asp Thr Met Leu 160

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205

<221> SIGNAL <222> -41..-1

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-10
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Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp

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Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Cys Ile Phe Lys Ile 10 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu 20 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 35 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu 55 60 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 70 75 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 85 90 Leu Pro Glu Glu Pro Lys Gly Thr Gln Met Leu Thr 100 105

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Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 185 190 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 200 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 215 220 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 235 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala Lys Lys Lys

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Met Phe Ala Pro Ala Val Met Arg Ala Phe Arg Lys Asn Lys Thr Leu -25 -20 Gly Tyr Gly Val Pro Met Leu Leu Leu Ile Val Gly Gly Ser Phe Gly -15 -10 -5 Leu Arg Glu Phe Ser Gln Ile Arg Tyr Asp Ala Val Lys Ser Lys Met 5 10 Asp Pro Glu Leu Glu Lys Lys Leu Lys Glu Asn Lys Ile Ser Leu Glu 20 25 Ser Glu Tyr Glu Lys Ile Lys Asp Ser Lys Phe Asp Asp Trp Lys Asn 35 40 Ile Arg Gly Pro Arg Pro Trp Glu Asp Pro Asp Leu Leu Gln Gly Arg 55 Asn Pro Glu Ser Leu Lys Thr Lys Thr Thr

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65

70

His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr 80 85 90 Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

95 100 105

His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
110 115 120

Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
125 130 135

Ile Gly
140

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Leu Gln Ala Ala Leu Leu Cys Val Asn Ala Ile Ala Val Leu His Glu -5 1 5 10 gag cga ttc ctc aag aac att ggc tgg gga aca gac cag gga att ggt 208 Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly Thr Asp Gln Gly Ile Gly 15 20 25 gga ttt gga gaa gag ccg gga att aaa tca sag sta atg avs ctt att 256 Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile 30 35 40 cga tct gta aga acc gtg atg aga gtg cca ttg ata ata gta aac tca 304 Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser 45 50 55 att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat 354 Ile Ala Ile Val Leu Leu Leu Leu Phe Gly 60 65 ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt 414 atatcttagc tggctgacct tgcacttgtc aaaaatgtaa agctgaaaat aaaaccaggg 474	agtaggaasg cgccgsccgt ggaggcgcca cgtcccttgc sgcggcggga gagamatcgc ttggacttcg gggcggcctc ggacggcc atg gcc ttt acc ctg tas tca ctg Met Ala Phe Thr Leu Xaa Ser Leu -10	
Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly Thr Asp Gln Gly Ile Gly 15 20 25 gga ttt gga gaa gag ccg gga att aaa tca sag sta atg avs ctt att 256 Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile 30 35 40 cga tct gta aga acc gtg atg aga gtg cca ttg ata ata gta aac tca 304 Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser 45 50 55 att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat 354 Ile Ala Ile Val Leu Leu Leu Phe Gly 60 65 ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt 414 atatcttagc tggctgacct tgcacttgtc aaaaatgtaa agctgaaaat aaaaccaggg 474	Leu Gln Ala Ala Leu Leu Cys Val Asn Ala Ile Ala Val Leu His Glu	160
Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile 30 35 40 Cga tct gta aga acc gtg atg aga gtg cca ttg ata ata gta aac tca 304 Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser 45 50 55 att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat 354 Ile Ala Ile Val Leu Leu Leu Phe Gly 60 65 ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt 414 atatcttagc tggctgacct tgcacttgtc aaaaatgtaa agctgaaaat aaaaccaggg 474	Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly Thr Asp Gln Gly Ile Gly	208
Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser 45 50 55 att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat 354 Ile Ala Ile Val Leu Leu Leu Phe Gly 60 65 ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt 414 atatcttagc tggctgacct tgcacttgtc aaaaatgtaa agctgaaaat aaaaccaggg 474	Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile	256
att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat 354 Ile Ala Ile Val Leu Leu Leu Phe Gly 60 65 ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt 414 atatcttagc tggctgacct tgcacttgtc aaaaatgtaa agctgaaaat aaaaccaggg 474	Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser	304
atatettage tggetgacet tgcacttgte aaaaatgtaa agetgaaaat aaaaccaggg 474	Ile Ala Ile Val Leu Leu Leu Phe Gly	354
	ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt atatcttagc tggctgacct tgcacttgtc aaaaatgtaa agctgaaaat aaaaccaggg	474

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              Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
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ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
                                                                  157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                  205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
                              35
get act tgc ecc ega gge ttc gec gtc acc gge tgc act tgt gge tec
                                                                  301
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
       45
                          50
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
                                                                  349
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
                      65
tgc gcg ggc atg gac tgg acc gga gcg cgc tgc tgt cgt gtg cag ccc
                                                                  397
Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
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517
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-5

ggtacgcgtt gctatacaga atctttggat atgtgcatca gtggtttatg ccaaattgtt

211

271

cca aat gaa caa ccc tgg ttg ttg aac tagcacctaa ggtcttarat

10

-10

Pro Asn Glu Gln Pro Trp Leu Leu Asn

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nate teres gete gacwaact tegga tegga tacc gcca	ggtogatgatgatgatgatgatgatgatgatgatgatgatgatg	ata ata atc aga gct aga aga	cctg ctgt actt cagg tact ccgc cgga gcta acat tcaa	ccgg ggtt aact gaga tgac tttc cgat caaa attt	ct c gc t t t gc t t c c c c t	gtcc attc gaar gctg gctg acag acag agat	gagg ccta ccaw tgga tcca gctc gcta ccaa ccatt	g t a c a g g c c a c c c c c c c c c c c c	rtat aagt ctcat cacc catcc aacc tcagt catc	aaat akac aggg agtcag ttgtg ttgtg agaca	ccc ata gga tgg attc gatg cta	akct ttaa tcat tcat taacg aacca actt ccat	ctc cctg ccat tcat ataa aggt	cgca tgta tgaa gaaw cata catct tcca tcca	aacrga accaaa ttaaaa aacagt tttcca attcgt caccga ctgaca cactat tgtcca aatagg	331 391 451 571 631 691 751 811 871 931 996
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Gly	Gln 1	Thr	Leu	Lys	Asp 5	Thr	Thr	Ser	Ser	Ser 10	Ser	Ala	Asp	tca Ser	Thr 15	152
Ile	Met	Asp	Ile	Gln 20	Val	Pro	Thr	Arg	Ala 25	Pro	Asp	Ala	Val	tac Tyr 30	Thr	200
Glu	Leu	Gln	Pro 35	Thr	Ser	Pro	Thr	Pro 40	Thr	Trp	Pro	Ala	Asp 45	gaa Glu	Thr	248
cca Pro	caa Gln	ccc Pro 50	cag Gln	acc Thr	cag Gln	acc Thr	cag Gln 55	caa Gln	ctg Leu	gaa Glu	gga Gly	acg Thr 60	gat Asp	gjà aaa	Pro	296
Leu	Val 65	Thr	Asp	Pro	Glu	Thr 70	His	Xaa	Ser	Xaa	Lys 75	Ala	Ala	cat His	Pro	344
act Thr 80	gat Asp	gac Asp	acc Thr	acg Thr	acg Thr 85	ctc Leu	tct Ser	gag Glu	aga Arg	cca Pro 90	tcc Ser	cca Pro	agc Ser	aca Thr	kac Xaa 95	392

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gtc Val	cat His	dac Xaa	aga Arg	ccb Pro 100	cba Xaa	kda Xaa	ccc Pro	tca Ser	akc Xaa 105	cat His	ctg Leu	gtt Val	ttc Phe	atg Met	agg Arg	44
atg Met	acc Thr	cct Pro	tct Ser 115	tct Ser	atg Met	atg Met	aac Asn	aca Thr 120	Pro	tcc Ser	gga Gly	aac Asn	sgg Xaa 125	Gly	tgt Cys	48
													Ser		gtg Val	536
gca Ala	agt Ser 145	gca Ala	ggc	agc Ser	tgt Cys	ccc Pro 150	ggt Gly	tat Tyr	gcc Ala	gga Gly	atc Ile 155	Ile	gca Ala	ggt Gly	gag Glu	584
				agg Arg		tgad	caac	etg	ctgg	gcac			ccaa	g		632
ggaa aac	agaca cctgo	aca g	gatga gccc	atgaa ctgaa	ag ct	tggaq ctaco	gccáq ctggq	g gg	ctgc cttg	cggt gggg	ccg ctg	agtc tccc	tcc tca	tacc	agagag tccccc atctcc	752
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	> 25 cago		sgco	egged	a go	c at	g ga	ıg ac	et ge	ga go	g ct	g cg	gg cg	gc co	g caa	53
a++	a.		**-				-2	:5				- 2	20		ro Gln	
Leu	Leu -15	Pro	Leu	ctg Leu	Leu	Leu -10	Leu	Cys	Gly	Pro	Ser -5	Gln	Asp	Gln	Cys	101
Arg 1	Pro	Val	Leu	cag Gln 5	Asn	Leu	Leu	Gln	Ser 10	Pro	Gly	Leu	Thr	Trp 15	Ser	149
ttg Leu	gaa Glu	gtg Val	ccc Pro 20	act Thr	Gly 999	aga Arg	gaa Glu	gga Gly 25	aag Lys	gaa Glu	ggt Gly	GJA aaa	gat Asp 30	cgg Arg	gga Gly	197
cca Pro	ggg ggg	cta Leu 35	akt Xaa	Gly 999	gcc Ala	Thr	cca Pro 40	gcc Ala	agg Arg	agc Ser	cct Pro	cag Gln 45	ggc	aag Lys	gag Glu	245
atg Met	999 Gly 50	aga	caa Gln	agg Arg	Thr	aga	aag	gtg Val	aag Lys	ggc Gly	cct Pro	qct	tgg Trp	akt Xaa	cac His	293

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gtg cca gtg ggg cat ctg gag ggt ggc acg gtc aag ctt cag aag gac Val Pro Val Gly His Leu Glu Gly Gly Thr Val Lys Leu Gln Lys Asp 85 90 95	389
acg ggc ctc cat tcc tgc ara gat ggt atg gct tct ctt gaa ggg acg Thr Gly Leu His Ser Cys Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr	437
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get gtc agt ctg acc aag etc gtc egg ggg agg aaa gee eet tte eet	501
Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala Pro Phe Pro 65 70 75	
gtt ggt gat tot ggg tot ggc ogt ggg ott dag oot agt oda gga tgt	549
Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser Pro Gly Cys	0.10
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Tyr Arg Tyr	
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kteetettet tgatggeget gaeetteete wtgteeteet teacettetg tggtkeette	718
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Glu Lys Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His	
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Ala Ala Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Leu Phe	203
1 5 10 15	
gac ctc tca gtg ctc aag ctc cac cac agc ctg cag vrr agt rag ccg	313
Asp Leu Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro	
20 25 30	
gac ctg cgg cac ctg gtg ctg gtc atr aac act ctg cgg cgc atc cag	361

Asp	Leu	Arg	His 35	Leu	Val	Leu	Val	Xaa 40	Asn	Thr	Leu	Arg	Arg 45	Ile	Gln	
gcg Ala	tcc Ser	atg Met 50	gca	ccc Pro	gcg Ala	gct Ala	gcc Ala 55	ctg Leu	cca Pro	cct Pro	gtg Val	cct Pro 60	acc	cca Pro	cct Pro	409
gca Ala	gcc Ala 65	CCC	ant Xaa	gtg Val	gct Ala	gac Asp 70	aac	tta Leu	ctg Leu	gca Ala	agc Ser 75	tcg Ser	gac Asp	gct Ala	gcc Ala	457
	tca													att Ile		505
ggc														cca Pro 110		553
cgt Arg	agc Ser	Ile	999 Gly	gga	wca Xaa	ccg Pro	ccc Pro	amc Xaa 120	ctg Leu	ggt Gly	gcc Ala	ttg Leu	gac Asp 125	ctg Leu	ctg Leu	601
		gcc	act											ctg Leu		649
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	gag Glu					ggc					ccg			gag Glu		745
gct	ccg	gag Glu	ctg Leu	gac Asp 180	gag	gcc Ala	gaa Glu	ttg Leu	gac Asp 185	tac	ctc Leu	atg Met	gat Asp	gtg Val 190	ctg Leu	793
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Asn Xaa Tyr Xaa Xaa Trp Gly Gln Gly Thr His Ser Ser Leu	
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Thr Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg
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cct Pro	ttc Phe	tcc Ser	tct Ser 5	ccg Pro	ggc Gly	act Thr	gac Asp	ccc Pro 10	acc Thr	ttt Phe	ccg Pro	tgt Cys	att Ile 15	tac Tyr	tgt Cys	152
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ttc	ctca	gga (cttc	ettt	gg ti	gggg	gattt	tac	ctttc	cca	aaag	gtate	gat (ctgai	ttctt	589 64 9
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gacagagatt ctcatga atg tgt cct gtg ttc tca aag cag ctg cta gcc	230
Met Cys Pro Val Phe Ser Lys Gln Leu Leu Ala	
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Cys Gly Ser Leu Leu Pro Gly Leu Trp Gln His Leu Thr Ala Asn His	
-10 -5 1 5	

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aga cag gtg tgg gga gag gtg cca gag ccc agt gat cgt tct gag gag

Arg Gln Val Trp Gly Glu Val Pro Glu Pro Ser Asp Arg Ser Glu Glu	
cct gag act cca gct gcc tac aga gcg aga act tgacggggtg cccgctgggg Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg Thr	493
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aat aaa ttt gga gca gaa gag ara agc ctt att gga ctt tct ggc att Asn Lys Phe Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile 10	146
ttc atc ggc att gga gaa att tta ggt gga agc ctc ttc ggc ctg ctg Phe Ile Gly Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu 20 25 30	194
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27	
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Gly Asn Ser Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu 100 105 110	
tat tot gaa rac age gee cea kea tit gee ate tit aat tit git cag 48	12
Tyr Ser Glu Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln	
115 120 125 130	
tot att tgc gca gcc gtg gca ttt ttc tac agc aac tac ctt ctc ctt 53	0
Ser Ile Cys Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu 135 140 145	
cac tgg caa ctc ctg gtc atg gtk atw ttt ggg ttt ttk gga aca att 57	18
His Trp Gln Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile 150 155 160	
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Ser Phe Phe Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly 165 170 175	
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Ser Asp Tyr Arg Ser Ile 180	
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tgc aca gtg agc att aaa ttt aca tac ttt cat gat ata cag act aat Cys Thr Val Ser Ile Lys Phe Thr Tyr Phe His Asp Ile Gln Thr Asn	10
-55 -50 -45 tot off aca aca tog aga cat tog aga tog aga tit tat tog goa tit 25	5 0
tgt ctt aca aca tgg aaa cat tcg aga tgc aga ttt tat tgg gca ttt 25 Cys Leu Thr Thr Trp Lys His Ser Arg Cys Arg Phe Tyr Trp Ala Phe	, 0
-40 -35 -30 -25	
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Gly Gly Ser Ile Leu Gln His Ser Val Asp Pro Leu Val Leu Phe Leu	

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ttg tta ata ttc ata tca atw kca ggt att ctg tat aaa ttc cas gat

255

Leu Leu Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp 30 303 gta ttg ctt tat ttt ccw kaa cag yya tcc tct tca cgt ctt tat gat Val Leu Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp 45 40 tcc cat gcc cac tgg cmt tcg rca taaaaaaaatt ttcatcagaa ccaaagatgg 357 Ser His Ala His Trp Xaa Ser Xaa aatacgtctg aatcttattt tgatacgata cactggagac aattcaccct attccccaac 417 tataatttat tttcatggga atgcaggcaa cataggtcac aggttggcca aatgcattac 477 537 ttatgttggt taacctcaaa gttaaccttt tgctggttga ttatcgagga tatggaaaaa gtgaaggaga agcaagtgaa gaaggactct acttagattc tgaagctgtg ttagactacg 597 657 tgatgactag acctgacctt gataaaacaa aaatttttct ttttggccgt tccttgggtg garcagtggc tattcatttg gcttctgaaa attcacatag gatttcagcc attatggtgg 717 agaacacatt tttaagcata ccacatatgg ccagcacttt attttcattc tttccgatgc 777 gttaccttcc tttatggtgc tacaaaaata aatttttgtc ctacagaaaa atctctcagt 837 gtagaatgcc ttcacttttc atctctggac tctcagatca attaattcca ccagtaatga 897 tgaaacaact ttatgaactc tccccatctc ggactaagan attagccatt tttccagatg 957 ggactcacaa tgacacatgg cagtgccaag gctatttcac tgcacttgaa cagttcatca 1017 aagaagtegt aaagageeat teteetgaag aaatggeaaa aaetteatet aatgtaacaa 1077 ttatataatg tttccctttt tgattattgc attgtatttt aatttgtgca gaatgataaa 1137 1197 quatgttect tttagaagtg tgttatgtet gtacetgtet gaagagtgae attaaaettt 1257 gaaaggactt cactgctcct ttacgatatt ccaaatagtt ttttacattg gaaaaactaa 1317 ttcttgggat tctttcatac attttcatca aaactttcag tgtgattatg tattcatatc ttcagtttaa tatgtcagta taatagatat tgttcaaaaag tttcttgttg ctaaagtggt 1377 gtaatctgtt acacagatga atagctagat gtggaaagag atatgtaaac aagaaacctt 1437 tgggtattgt ttcttaagta aatattggga caatcatggt aagcaaactt agttctgtaa 1497 1557 ctgcattttt caccttaaaa qttaaatgaa atgcatgatg gtattttatt ccttgaatta 1617 tgcaatgcaa cattttacat gtaaatagca ctggtcatat actgatgtat atggttatct gggttatatc tatttttatg taaactctat ttttgttttt ggcaagaagt gaaattgaga 1677 1737 cttatgtgca ggttgccatt gaattttgct ctggtgaatg ctgagatcca gctttttctt 1777 acaaataaat gggaccctgt tttccaaaaa aaaaaaamcm

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Thr	Gly	Pro	Trp	Gly	Ala	Val	Ala	Thr	Ser	Ala	Gly	Gly	Glu	Glu ·	Ser	
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AIG	****	Val	50	Cys	2 .110	110		55				-1-	60			
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Ser	Glv	Asn	Glu	Thr	His	Phe	Thr	Gly	Asn	Glu	Val	Gly	Phe	Phe	Lys	
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Asn	IIÞ	GIU	Pro	ASII												
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cct tagettetgg geetatesge tgeetteect ettytteeta ceaectette Pro	434
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cacificating grayereac cracerees	Met Asp Glu Tyr
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Ser Trp Trp Cys His Val Leu Glu V	
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Phe Ile Asn Ile Thr Leu Trp Leu G	ly Ser Leu Cys Gin Arg Phe Phe
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Tyr Ala Ser Gly Thr Tyr Phe Leu I	le Tyr Ile Ser Thr Val Thr Pro
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1013

1073

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Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu Ser Gln Pro Gly Pro Ser

185 190 195 tee etg atg eee gtg etg gge tak gat eet eet eag ete tat etg aeg Ser Leu Met Pro Val Leu Gly Xaa Asp Pro Pro Gln Leu Tyr Leu Thr 205 210 cag etc arg gag gee tit ggg gat etg gee ett tie tie tat gae cag 824 Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala Leu Phe Phe Tyr Asp Gln 220 225 cat ggt gga gag gtg att ggt gtc ctc tgg aag ccc acc agc ttc cag 872 His Gly Gly Glu Val Ile Gly Val Leu Trp Lys Pro Thr Ser Phe Gln 235 240 ccg cag ccc ttc aag gcc tcc agc aca aag ggg cgc atg gtg atg tct 920 Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys Gly Arg Met Val Met Ser 255 cga ggt ggg gag cta gta atg gtg ccc aat gtt gaa gca atc ctg gag 968 Arg Gly Glu Leu Val Met Val Pro Asn Val Glu Ala Ile Leu Glu 270 gac ttt gct gtg ctg ggt gaa ggc ctg gtg cag act gtg gag gcc cga 1016 Asp Phe Ala Val Leu Gly Glu Gly Leu Val Gln Thr Val Glu Ala Arg 285 290 agt gag agg tgg act gtg tgatcccagc tctggagcaa gctgtagacg 1064 Ser Glu Arg Trp Thr Val 295 gacagcagga cattggacct ctagagcaag atgtcagtag gatgacctcc accctccttg gacatgaatc ctccatggag ggcctgctgg ctgaacatgc tgaatcatct ccaacaaaac ccagccccaa ctttctctct gatgctccag cattggggca ggggcatggt ggcccatgta gtctcctggg cctcaccatc ccagaagagg agtgggagcc agctcagaga aggaactgaa cccaggagat ccatccacct attagccctg ggcctggacc tccctgcgat ttcccactcc tttcttagtc ttcttccaga aacagagaag gggatgtgtg cctgggagag gctctgtctc 1424 cttcctgctg ccaggacctg tgcctagact tagcatgccc ttcactgcag tgtcaggcct 1484 ttagatggga cccagcgaaa atgtggccct tctgagtcac atcaccgaca ctgagcagtg 1544 gaaaggggct atatgtgtat gaatagacca cattgaagga gcaaaaaaaa aaamcch 1601

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Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser

-15

-10

158

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aga cac cac ata ctg cag cag ttc cta gtg aga aaa tct gtg cca cta 206 . Arg His His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu 15 20 254 gaa aat get tea ett eea tit eet eae etg gge agt tet etg tit aaa Glu Asn Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys 3.0 35 40 303 att gtg ggc tgatttggtc ttcctctcct cctcccactg ttactgccct. Ile Val Gly 45 gragecettg ttraggtgta ragarcetta ttrtggrete tagtgtrett gtrtgtratg 363 acacaccett cegeceaaat acetetgace ecaaggetgg aatggggetg gtaggarata 423 agtttgetta eteatartea tgteetttet ettggeaeet getteeetge ggtgteetea aatggattte tgtgtggcag tggartgatt gcatgaattt ttetgtaaca cattaaettt 543 gtattattat taagggartt tgaraaagct ttgcttataa tgtcaaggca aggaggtaaa 603 aactggagcc caaakaaatt cccttagggc aagattatgt tataataraa aattgaattt 663 cctgaggcag tggctgccac cccttttcar atgtttagtc ctgcaaatag catctttctt 723 gtagtctgtg acatggatgg ggatgctagg gcccttaggg gcaaggggac taaactaaat 783 caakttgagt ttttttccag caggggttar gggaggtact csctgttgat atttgacact 843 araaagtaat cttttttaca aaactgtttt tctaggtggg tggaaagtga aactgccaca 903 tccttgttgg tttagtccaa raratcattt gcaacaacag taratgtccg ggttttgttt 963 ctgtcttttt attatgaaaa actatgttaa gggggaaaat gtggattatg gtaaccarag 1023 gaatccctas ccttgttttc cttaraarac ttgtttagtg ttttatcara cgtctgttgt 1083 agttgtarac aggaaagctt gtgaraaaaa caccacatgg ascctgtaaa tgtttttgca 1143 caacctgtaa agcattcttg gaaktggcca gtaaaaaggg gttttaccat ttaaaaaaaa 1203 1206

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	Tyr 5	HIS	TÀT	rne	GII	11p	Arg	Arg	Ala	GIN	arg 15	GIII	Ala	Ala	GIU .	
	cag					atc		taga	acto	agg 9		tttt	c t	cctga	igcar	315
	gccc	aa g	gcat	gctg	gt gg	gagag	gactt	cad	ctg	cac	catt	tcca	agg	tcaad	aggac	375
	_	_					-		_						gttct	435
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ccta															_	536
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								met	пÀг	-	val	ьеи	ьеи	Leu		
										-15					-10	3.63
														gac		163
THE	Ala	TTE	ьeu		vaı	Ala	vaı	GIY		Pro	vai	ser		Asp	GIN	
				-5					1				5			200
														tca		209
GIU	Arg		ьys	Arg	Ser	TTE		Asp	ser	Asp			Ата	Ser	GIÀ	
		10					15					20				0.55
														cca		257
Aaa		vaı	Pne	Pro	ıyr		Tyr	Pro	Pne	Arg		ren	Pro	Pro	TTE	
	25					30	4. 4. 4.				35					
			_						-					cca		305
	Pue	Pro	Arg	Pne		Trp	Pne	Arg	Arg		Pne	Pro	lie	Pro		
40					45					50					55	
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PIO	GIU	ser	Ala		Thr	Thr	PLO	ьeu		Ser	Glu	Lys				
				60					65							
															araat	414
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Met T	Thr Cys Arg Gly Ser
	-25
tgc agc tac gct acc agg aga tct cca agc gaa	ctc agc ctc ctc cca 161
Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu	
-20 -15	-10
age tee etg tgg gte eta gee aca age tet eca	
Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro	Thr Ile Thr Ile Ala
-5 1	5
ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt	cca tca tca tkt cgt 257
Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu	Pro Ser Ser Xaa Arg
10 15 20	25
crc aaa agg cgc tgg tgt cag gca asc car caa	ara gct ctg ctg 302
Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln	
30 35	40
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	Met Val Pro Trp Pro
	-55
agg ggc aag gtg aaa act gct cct att ccc atc	
Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile	_
-50 -45	-40
ctc cct acc cac gac cca ccc acc cca gca cat	tgg tct cca gca tct 271
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His	Trp Ser Pro Ala Ser
-35 -30 -25	-20
cat cag cag ttt aaa cat kkg tca ccc ctc ctc	
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu	
-15 -10	-5
ggt cag tgc tct ctg ttc arc aat ttg agg aaa	
Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys	
1 5	10
	ccc ctg aca ctc tgg 415

Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu Pro Leu Thr Leu Trp 15 20 25	
cca tta act cct caa ttt gct gag ctc act aca gtg gca caa aaa aaa Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr Val Ala Gln Lys Lys 30 35 40 45	463
ttg agg tgg tcc ggg acc cta ggt tgg ggt cca gtt ccc agc tgg gtt Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro Val Pro Ser Trp Val 50 55 60	511
caa ttt ttt tta ggg tgaatggagg garagttggg gactgaaaas ccttcaaara Gln Phe Phe Leu Gly 65	566
caatgttatt acagcaktot cocottatoo aaaktttoot tttootgadt ttoagttago	626
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coctcaggat aaagtotgga cocctcago atg got tgt gag act cat ggt gto	233
Met Ala Cys Glu Thr His Gly Val	233
-30 -25	
ott gte eet get eac ete tet ggt ete ate aet tge ett ett gea tte	281
Leu Val Pro Ala His Leu Ser Gly Leu Ile Thr Cys Leu Leu Ala Phe -20 -15 -10	
gg gtc cca gcc tcc tgt atc cag aga tgc agt ggc tct cca ttg cca	329
Trp Val Pro Ala Ser Cys Ile Gln Arg Cys Ser Gly Ser Pro Leu Pro	323
-5 1 5 . 10	
etc tgatteetee tttettttgg teacagagaa agggtaettt etetgteaaa Seu	382
cctcaactta gacttgactt cctccaagga gctttggcta tactctctcc cwcgaccccc	442
accetggeat actacacara teactetggg eteacttgee tgeetaatgg teateteece	502
agtaaactgt aagcteettg agggeaagga ttgtgttgga atttttgtat taacagtgee	562
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tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                    Met Ala Pro His Thr Ala Ser
                                        -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
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Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
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                                     -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
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gettecetan ecctgaette ccaageetta gteateacce teteteccae ccagggetea
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gca gac tca act gag aag tca gcc tct gcg gca ggc acc agg aat ctg Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr Arg Asn Leu -45 -40 -35	154
cct ttt cag ttc tgt ctc cgg cag gct ttg agg atg aag gct gcg ggc Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys Ala Ala Gly -30 -25 -20 -15	202
att ctg acc ctc att ggc tgc ctg gtc aca ggc gtc gag tcc aaa atc Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu Ser Lys Ile -10 -5	250
tac act cgt tgc aaa ctg gca aaa ata ttc tcg agg gct ggc ctg gac Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala Gly Leu Asp 5 10	298
aat cyg agg ggc ttc agc ctt gga aac tgg atc tgc atg gcg tat tat Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met Ala Tyr Tyr 20 25 30	346
gag agc ggc tac aac acc aca gcc car acg gtc ctg gat gac ggc agc Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser 35 40 45 50	394
atc gac tay ggc atc ttc caa atc aac agc ttc gcg tgg tgc aga cgc Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg 55 60 65	442
gga aag ctg aag gag aac aac cac tgc cay gtc gcc tgc tca gcc ttg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys Ser Ala Leu 70 75 80	490
rtc act gat gac ctc aca gat gca att atc tgt gcc arg aaa att gtt Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa Lys Ile Val 85 90	538
aaa gag aca caa gga atg aac tat tgg caa ggc tgg aag aaa cay tgt Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys Lys His Cys 100 105 110	586
gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser 115 120 125	631
taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc caaatgcctg tgtcatcttg tcccgtttcc tcccaatatt ccttctcaaa cttggagagg gaaaattaag ctatactttt aagaaaataa atatttccat ttaaatgtca amaaaaaaaa ah	691 751 811 813

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Asn	Glu	Thr	Ile	Ile	Val	Leu	Pro -55	Ser	Asn	Val	Ile	Asn -50	Phe	tcc Ser	Gln	222
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			aaa										cta	ttg Leu		894
tct Ser	taa		aaa q	gga	gaaat	ta t		cagaa	a agt	tgat	tct		gataa	ata		947
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ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                                                                  172
                          Met Gln Val Pro His Leu Arg Val Trp
                              -35
                                                 -30
aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
                                                                  220
Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg Asn Leu Gly Phe Thr
        -25
                           -20
agt atg tgc ata ttg ttc cac tgt ctt ctt agc ttt cag gtt ttc aaa
                                                                  268
Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
aag aaa aga aaa ctt ara ctt ttc tgatgttctt ttttacgtaa ataaccattt
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Lys Lys Arg Lys Leu Xaa Leu Phe
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Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp -10 -5 1	
	218
tgt gac cca cgg agg atc cac tcc cag gat gac gtg ctc cgt agc tct Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser	210
5 , 10 15	
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tgg aga agg tca caa ccc ttc tct gtt ggt ctg cct tct gct gaa aga	314
Trp. Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg 35 40 45	217
ctc gag aac caa cca ggg aag ctg tcc tgg agg tcc ctg gtc gga gag	362
Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu 50 65	
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Gly His Arg Ile Cys Asp Leu	
70	473
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ate cca gtt cct cca agg ggc ctg ggt gct ggg gag ggg tca ggt agt	158
Ile Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser	100
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Pro Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu	

20	
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gto ttt too acc act ggo coa goo ctg ctg ctt ctg gto ago tto	302
Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe	
ctc acc ttt gac ctg ctc cat agg ccc gca gtc aca ctc tgc cac agc	350
Leu Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser	
25 30 35	
gca aac ttc tca cca ggg gcc aga gtc agg ggg ccg gtg aag gtc ctg	398
Ala Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu 40 45 50	
40 45 50 gac age agg ctc tac tcc tgc aaa tgg gta cag tct cag gac aac	446
Asp Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn	
55 60 65	
tta gcc tcc agg aag cac tgc tgc tgc tca tgg ggc tgg gcc cgc	494
Leu Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg	
70 75 80 85	547
tcc tgaaaacctg tggcatgccc ttgwaccctg cttggcctgg ctttctgcct Ser	34,
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Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly	
-10 -5 1	
tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag	153
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys 5 10 15	
5 10 15 gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac	201
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp	
20 25 30 35	
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caa gee ege ace eee aac gag geg gee eee eee age gag geg	249
Gln Val Cys Ile Ser Asn Glu Val Val Ser Phe Ser Glu Ser Pro	249

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55 60 65	
cct ctc wkc gac tta bct atg act cct cgg ckc ycc agg gcc tgg ggc 34!	5
Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg Ala Trp Gly 70 75 80	
cck gtg ggt ccd aaa gtg cct cct gct gtc tct ccc gcg ctg ggc tcg 39	3
Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala Leu Gly Ser 85 90 95	
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Gly Glu His Pro Xaa Xaa 100 105	
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tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag 153	3
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys	
5 10 15 gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac 203	1
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp	-
25 30 35 caa gtc tgc atc tcc aac gag gtg gtc gtc tct ttt aaa tgg agt gta 249	٥
Gin Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys Trp Ser Val	J
40 45 50	_
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55 60 65	

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Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly Val Ile Thr	345
70 75 80	
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85 90 95	
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Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln Asp Pro Ser	
100 105 110 115	400
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120 125 130	
ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga	534
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raa agg aca aaa tat gaa aca cca aga aaa rga raa gga aaa aaa gga Xaa Arg Thr Lys Tyr Glu Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly 30 35	435
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Ile 140	Val	Gln	Tyr	Ser	Pro 145	His	Cys	Lys	Leu	Ile 150	Ile	Val	Ser	Asn	Pro 155	
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Val 220	Asn	Ile	Ala	Gly	Val 225	Pro	Leu	Lys	Asp	Leu 230	Asn	Ser	Asp	iie	G1y 235	
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Thr	Asp	Lys	Asp	Pro 240	Glu	Gln	Trp	Lys	Asn 245	Val	His	Lys	Glu	Val 250	Thr	
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rat			gta	ttc	ctc			cct	tat	atc		qqa	gag	aac	ggt	1117
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Phe Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val 85 90 95									
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Gly Arg Arg Pro Ser Xaa His Pro Gly Arg
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Met	Asn	Xaa	Tyr		Ser	Pro	Phe	Asn		Gln	Leu	хаа	Tyr	Terr.	Add	
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Cys	Leu	His	Leu	Ala	Leu	Val	Tyr	Tyr	Asp	Phe	Phe	Gln	Met	Phe	Pro	
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PCT/IB98/02122 -

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622

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Met Xaa Leu Val Leu Gly Lys Leu Ser Gln 15 20	
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gcc cca gga tca acc cag cac cga aga aaa aca acc aga aga	375
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cag cag cca ggt tcc ctc acc cca agc tca ccc act gtt ggg gag att Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu Ile -40 -35 -30	152
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ggg ggg	Leu	act	gtg Val	gcc Ala	cca Pro	ccc Pro 30	caa	gcc Ala	gtc Val	agc Ser	ctc Leu 35	cag	ggw Gly	atc Ile	tac Tyr	344	Ł
Thr	25 ctg Leu	cct Pro	tgg Trp	ctg Leu	Leu	cag	ctt Leu	ttt Phe	cac His	tcc Ser 50	act	gcc Ala	cta Leu	rgg Xaa	gna Xaa 55	392	2
40 dtt Xaa	cag Gln	caa Gln	cct Pro	aat Asn	45 gga Gly	tct Ser	cta Leu	tct Ser	Leu	aac	atc Ile	tct Ser	tca Ser	tcc Ser 70	cat	440)
gct Ala	ccr Pro	rgt Xaa	Pro	60 rca Xaa	acc Thr	tgc Cys	acc Thr	Leu	65 gaa Glu	cca Pro	gga Gly	gtg Val	Asp	cct	acc Thr	488	3
cga Arg	sct Xaa	Val	75 tgt Cys	att Ile	aat Asn	ccc Pro	His	80 ccc Pro	cca Pro	cca Pro	cca Pro	Ile	85 tta Leu	aaa Lys	abc Xaa	536	5
cct Pro	Leu	90 tcc Ser	ccc Pro	tac Tyr	cct Pro	Lys	95 ccc Pro	cag Gln	tta Leu	ggt Gly	Thr	100 cat His	gct Ala	ggy ggg	caa Gln	584	1
Val	105 aat Asn	taad	caatt	cta t	gca	110 caggi	ca ct	agti	ttai	t tg	115 tatta	accg	ttc	cagg	gta	640)
atco gcct ggca ggat	cago agaco agaco	cac f caa (gtc f gag (tttgg caggg tgtrg gttg	ggagg gtgaa gtcc	gc ca aa co ca go ga go	aaggi cccgi ctati ccga	tggg tctc tcag gatt	c aga t aca g aga	atcgo aaaa actgo	cctg atar aggc	aggi gaaa acga	tctg aatt: agaa	gag (rgc (ttc (ttca: cagg catg	cctgta agacca tgtggt aaccca acagag	760 820	
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Larg	Glu	TYD	Thr	Ser	LVS	Leu	Trp	His	Arq	Gln	Ser	Ile	Val	Val	Ser	
Буз	-25	LLP	****	001		-20			• •		-15					
		ata	cta	ctt	act		ctt	ata	act	acσ	tat	tat	gtt	gaa	gga	363
27-	Tan	Tan	Tou	Tou	מומ	222	T.AU	Tle	Δla	Thr	Tyr	Tyr	Val	Glu	Glv	
	neu	Den	neu	neu	-5	Gry	Deu	110	nια	1	- , -	+ J +		5	,	
-10					_	•••	-a-	- - -	~		C2.0		ctt	tta	tat	411
grg	cat	Caa	cag	Lat.	949	Caa	722	Tla	Glu	Larc	Cla	Dhe	Leu	T.e.ii	Tur	
vai	HIS	GIN		Tyr	vaı	GIII	Arg		Gru	шуs	GIII	FIIC	20	DCu	- 7 -	
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yal Yal	222	Tle	Glu	Acn	Ara	Thr	Len	Tvr	Phe	Phe	Len	Lvs	Arg	Leu	Leu	
AGI	OLY	226	U-u	155		****		-1-	160			-,-	5	165		
266	+		~++			ct c	taaa	assa.		acto	ctaa	agt	aaaa		aaaaa	901
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Asn	Phe	Leu	Leu	Ile	Leu	Thr	Ile	Leu	Thr	Ile	Trp	Leu	Phe	Lys	Asn	
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nea	лаа	25	Gly	neu	110		30	-] -				35				
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	40						~~~		a++	+-+		+ = +	222	tac	227	458
act	ctg	ctg	gtt	aat	atc	mb-	yac	Caa	77-1	The w	Clu	m.v.	Tare	Tire	Tare	100
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Pro	Pro	Ile	Ile	Phe	His	Ala	Gly	Tyr	Ser	Leu	Lys		Arg	His	Phe	
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213

Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His Ser Glu aca tat tgc atg ttt caa gac aag aag tac aga gtg ggt gag aga tgg 261 Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu Arg Trp 309 cat cct tac ctg gaa cct tat ggg ttg gtt tac tgc gtg aac tgc atc His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn Cys Ile 30 . 35 tgc tca gag aat ggg aat gtg ctt tgc agc cga gtc aga tgt cca aat 357 Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys Pro Asn 45 50 gtt cat tgc ctt tct cct gtg cat att cct cat ctg tgc tgc cct cgc 405 Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys Pro Arg 60 65 450 tgc cca gaa gac tcc tta ccc cca gtg aac aat rwg gtg acc agc Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser 80 tagtottgok agtacaatgg gacaacttac caacatggas agctgttogt agctgrrggg 510 ctctttcaga atcggcaacc cmatcaatgc acccagtgca gctgttcgga rggaaacktg 570 tattgtggtc tcaagacttg ccccaaatta acctgtgcct tcccagtctc tgttccarat 630 tectgetgee gggtwtgeag argagatgga caactgteat gggaacmtte tgatggtgat 690 atottocggo aacotgocaa cagagaagoa agacattott accacogoto toactatgat 750 cetecaceaa geegaeagge tggaggtetg teeegettte etggggeeag aagteaeegg 810 ggagctctta tggattccca gcaagcatca ggaaccattg tgcaaattgt catcaataac 870 aaacacaagc atggacaagt gtgtgtttcc aatggaaaga cctattctca tggcgagtcc 930 tggcacccaa acctccgggc atttggcatt gtggagtgtg tgctatgtac ttgtaatgtc accaagcaag agtgtaagaa aatccactgc cccaatcgat acccctgcaa gtatcctcaa 1050 aaaatagacg gaaaatgctg caaggtgtgt ccaggtaaaa aagcaaaaaa aaaaaa 1106

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- 5

-10

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-15

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Thr Leu Ile Ala	20 ccc aga tgg ctc Pro Arg Trp Leu	25 ctg aca gca Leu Thr Ala	30 gcc cac tgc ctc aag Ala His Cys Leu Lys 45	311
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ggc tgt gag car	acc cgg aca gcc	act gag tcc Thr Glu Ser	ttc ccc cac ccc ggc Phe Pro His Pro Gly 75	407
ttc aac aac agc		-	aat gac atc atg ctg Asn Asp Ile Met Leu 95	455
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Thr Leu Ser Ser	Arg Cys Val Thr	Ala Gly Thr	agc tgc ctc att tcc Ser Cys Leu Ile Ser 125	551
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Arg Cys Ala Asn 145	Ile Thr Ile Ile 150	e Glu His Gln	aag tgt gag aac gcc Lys Cys Glu Asn Ala 155	647
Tyr Pro Gly Asn 160	Ile Thr Asp Thr	Met Val Cys-	gcc agc gtg cag gaa Ala Ser Val Gln Glu 175	695
Gly Gly Lys Asp	Ser Cys Gln Gly 180	Asp Ser Gly 185	ggc cct ctg gtc tgt Gly Pro Leu Val Cys 190	743
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	-		tggattcaaa ttctgccttg	1066
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	t Pr					s Cy					a Va				y Leu -10	
tta	ctc		ggt													97
Leu	Leu	Gly	Gly	Gly -5	Gly	Val	Tyr	Gly	Ser 1	Arg	Phe	Arg	Phe 5	Thr	Phe	
			aga Arg													145
			atg													193
_	25		Met			30					35					
			tgc Cys													241
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			aaa													337
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Asn	Asn 105	Asn	Arg	Asp	Leu	Ser 110	Met	Val	Arg	Met	Lys 115	Ser	Met	Phe	Ala	
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	Gly	Phe	Cys	Phe		Ala	Leu	Met	Gly		Phe	Asn	Ser	Ile		
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Ser	Phe	11e 170	Phe	Leu	Xaa	Ile	Leu 175	Cys	Thr	Met	Ser	11e 180	Arg	GIn	Asn	
	_	_	att				-			_	_	_			_	673
Ile	Gln 185	Lys	Ile	Leu	Gly	Leu 190	Ala	Pro	Ser	Arg	Ala 195	Ala	Thr	Lys	Gln	
gca		gga	ttt	ctt	ggc		cca	cct	cct	tct		aag	ttc	tct		718
	Gly	Gly	Phe	Leu	_	Pro	Pro	Pro	Pro		Gly	Lys	Phe	Ser		
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aca atc gca aaa tyc rrg gcs tva gag ggc ctc cga gac ccc tat ggc Thr Ile Ala Lys Xaa Xaa Ala Xaa Glu Gly Leu Arg Asp Pro Tyr Gly -80 -75 -70	160
cgc ctc tgt ggt agc gag cac ccc cga aga cca cct gag cgg ccc gag Arg Leu Cys Gly Ser Glu His Pro Arg Arg Pro Pro Glu Arg Pro Glu	208
-65 -60 -55  gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala	256
-65 -60 -55  gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala -50 -45 -40  tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe	256 304
gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala -50  tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35 -30 -25 -20 cag ggc acc aag aaa agt ctc ctg atg tct ata tta gcg ctc atc ttc Gln Gly Thr Lys Lys Ser Leu Leu Met Ser Ile Leu Ala Leu Ile Phe	
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gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala -50 -45 -40  tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35 -30 -25 -20  cag ggc acc aag aaa agt ctc ctg atg tct ata tta gcg ctc atc ttc Gln Gly Thr Lys Lys Ser Leu Leu Met Ser Ile Leu Ala Leu Ile Phe -15 -10 -5  atc atg ggc aac agc gcc aag gaa gct ctg gtc tgg aaa gtg ctg ggg Ile Met Gly Asn Ser Ala Lys Glu Ala Leu Val Trp Lys Val Leu Gly 1 aag tta gga atg cag cct gga cgt cas cac agc atc ttt gga gat ccg Lys Leu Gly Met Gln Pro Gly Arg Xaa His Ser Ile Phe Gly Asp Pro	304 352
gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala -50  tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35  cag ggc acc aag aaa agt ctc ctg atg tct ata tta gcg ctc atc ttc Gln Gly Thr Lys Lys Ser Leu Leu Met Ser Ile Leu Ala Leu Ile Phe -15  atc atg ggc aac agc gcc aag gaa gct ctg gtc tgg aaa gtg ctg ggg Ile Met Gly Asn Ser Ala Lys Glu Ala Leu Val Trp Lys Val Leu Gly 1  aag tta gga atg cag cct gga cgt cas cac agc atc ttt gga gat ccg	304 352 400

ccc cga gca cac gtg gaa tcg agc ara ctg aaa stc wtg cat ttt gtg Pro Arg Ala His Val Glu Ser Ser Xaa Leu Lys Xaa Xaa His Phe Val 65 70 75	592
gca agg gtt cgt aac cga tgc tct aaa gac tgg cct tgt aat tat gac Ala Arg Val Arg Asn Arg Cys Ser Lys Asp Trp Pro Cys Asn Tyr Asp 80 85 90	640
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gtk atg aac agc cgt ggc atc tgg ctc tcc tac gtg ctg gcc atc ggt Val Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly -20 -15 -10	155
ctc ctc cac atc gtg ctg ctg agc atc ccg ttt gtk agt gtc cct gtc Leu Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val -5 1 5	203
gtc tgg acc ctc acc aac ctc att cac aac atg ggc atg tat atc ttc  Val Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe  10 20	251
Ctg Cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys 25 30 35 40	299
gcg agg ctg cta acc cac tgg tgagcagatg gattatgggg tccagttcac Ala Arg Leu Leu Thr His Trp 45	350
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ctg ctt cta atc acc cct tct ccc agc cct ctt cta ttt gat aga ggt Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -10 -5 1 5 ctg tcc ctc aga tca gca atg tct tagcccctct cctctctcc attccttcct	394 448
Leu Ser Leu Arg Ser Ala Met Ser  10 gttggtactc atttcttcta acttttaata aacatttagg tataatacat tacagtaagt gctatttaga tacaaactta aaacatacta tatattttaa ggatctaaga atcctttara rrrggcacat gactgaagta cctcagctgc gcagcctgta accagtttt ttaatgtaaa agtaaraatg ccagccttaa cctabccctg carataaaag ctaacttta ttaataccag ccctgaataa tggcactaat ccacactctt ccttaragtg atgctggaaa aataaaatca ggggcttcag attaaaaaaa aaa	508 568 628 688 748 771

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atg aat cag ttc cta att gat ata tct agc ttt acc tcc cga gtt aaa  Met Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys  20 25 30	326
aaa aaa atc ttt tta ttt tat gcc ttc awa ggt tgc ycg ttt car agt Lys Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser 35 40 45	374
gcc aca taaataaaat gtttaacaaa aaaaaaaaa Ala Thr	409
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Gly Ile Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe	
-5 1 5	. 2
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get gtc ttg cca acc atg act get ttt geg age ggc ctg gga ggt gaa	350
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Gly Xaa Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu	
40 45 50 55	
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Gly Arg Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln 60 65 70	
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Gly Trp Ala Leu	
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Met Gly Trp Gln Arg	
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Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser Ala His Pro Pro Gln	
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Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp Val Gly Ile Cys	
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gcaagettae caaggaggag ategttgaca agtatgaett atttgttgge agecaggeca	180
cagattttgg ggaggeetta gtaegge atg atg agt tet gag eta egg agg aac	234
Met Met Ser Ser Glu Leu Arg Arg Asn	
-25	
cct cat ttc ctc aaa agt aat tta ttt tta cag ctt ctg gtt tca cat	282
Pro His Phe Leu Lys Ser Asn Leu Phe Leu Gln Leu Leu Val Ser His	
-20 -15 -10 -5	
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Glu Ile Val Cys Ala Thr Glu Thr Val Thr Thr Asn Phe Leu Arg His	

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ratttacacw wtgtattatg tattaacatg gcgtgtttat ttttgtattt ttctctggtt	499
gggagtatka tatgaaggat caarateete aacteacaca tgtaracaaa cattasetet	559
ttactctttc tcaacccctt wtatgatttt aataattctc acttaactaa ttttgtaagc	619
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aa	1641
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cct tcc cca atg ccc cag cta cct cct gat acc ctt gag atg egg gtc	158
Pro Ser Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val	
-35 -30 -25	
Cga gat ggc agc aaa att cgc aac ctg ctg ggg ttg gct ctg ggt cgg Arg Asp Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg -20 -15	206
-20 -15 -10	_

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254

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act		aas	aad	act	atc		tac	act	gag	_	atc	aaq	caa	cgg		302
Ala	Ala	Gly	Lys	Ala 15	Val	Ser	Cys	Ala	Glu 20	Ile	Val	Lys	Arg	Arg 25	Val	• • • • • • • • • • • • • • • • • • • •
cca	aac	cta	cac		ctc	acc	aad	cta		ttc	ctt	саа	act	gag	gac	350
Pro	Gly	Leu	His	Gln	Leu	Thr	Lys	Leu 35	Xaa	Phe	Leu	Gln	Thr 40	Glu	Asp	
agc	tgg	gtc		scc	tca	cct	gac	aca	ggg	cta	rac	ccc	ctc	aca	gtg	398
														Thr		
cgc	cgc	cat	gtg	cct	gca	ktg	tgg	gtg	ctg	ctc	asc	cgg	gac	CCC	ctg	446
Arg	Arg 60	His	Val	Pro	Ala	Xaa 65	Trp	Val	Leu	Leu	Xaa 70	Arg	Asp	Pro	Leu	
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75				_	80	_				85				Gly	90	
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Gly	Ser	Met	Pro	Ser 95	Ser	Ser	Cys	Gly	Pro 100	Arg	Ser	Xaa	Lys	Arg 105	Ala	
cra	rac	acc	cga	tcg	tgaa	aaac	ctg d	ctgas	scca	gc ct	gtt	ctcc	g gg(	cctra	aatg	597
Xaa	Xaa	Thr	Arg 110	Ser												
_		_		-			_								caaggt	657
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tgt	aatg	caa 🤉	gtcc	ccta	ac to	ccct	gtt	g cta	acat	taa	ctt	cctta	aag 1	taata	aatcaa	120
tga	aaga [,]	vat 1			His (					lle S				gag g Glu (		169
										ttg	ttt			act Thr		217
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ctg	cat	tgc	ttc		gac	ctc	ccc	act		atg	cct	cta	ara	gcc	aaa	313

Leu His Cys Phe Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys	
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aat arg ggt ggt gat aga aag gtt gaa raa raa atg aar aag cac gga	542
Asn Xaa Gly Gly Asp Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly	•
90 95 100 105	
agt wet cat atg gga tte cea raa aac etg met aac ggt gee aet get	590
Ser Xaa His Met Gly Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala	
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Asp Asn Gly Asp Asp Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro	
125 130 135	
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Glu Ser Xaa Gln Phe Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp	
140 145 150	
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Phe Ser Gly His Pro Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln	
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Leu Val Leu Ala Ala Ala Ala Gly Ala Val Ala Val Phe Leu Ile Le	au .
-10 -5 1 5	
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Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr Pro Arg Glu Se	er
10 15 20	
ctc agt atc ttg gta gtg gct ggg tcc ggt ggg cat acc act gag a	cc 201
Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His Thr Thr Glu I	le
25 30 35	
ctg agg ctg ctt ggg agc ttg tcc aat gcc tac tca cct aga cat ta	at 249
Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser Pro Arg His T	yr
40 45 50	
gtc att gct gac act gat gaa atg agt gcc aat aaa ata aat tct t	tt 297
Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys Ile Asn Ser P.	ne

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+00	200	a++	<b>+1/</b> 0		200	++~	~~~						1-			447
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ser	inr	vaı		Thr	Thr	Leu	HIS		Met	Trp	Leu	Ser		Pro	ren	
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Cys	Val	Pro	Ile	Cys	Val	Ser	Ala	Leu	Leu	Leu	Gly	Ile	Leu	Gly	Ile	
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Lys	Lys	Val	lle	Ile	Val	Tyr	Val	Glu	Ser	Ile	Cys	Arg	Val	Lys	Thr	
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	cag Gln 30															314
Ile 45	gac Asp	Arg	Glu	Asn	Phe 50	Val	Asp	Ile	Val	Xaa 55	Ala	Lys	Leu	Lys	Ile 60	362
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	ggt Gly															458
Let	aag Lys	Asp 95	Gly	Gln	Gln	Ile	Pro 100	Val	Phe	Lys	Leu	Ser 105	Gly	Glu	Asn	506
	gat Asp 110	-			_		taga	agac	gac (	ccaga	aaga	ec ca	agcti	tgcti	t	557
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CCa aaa aac gtg agg tgc tct act tgt gat tta agg aaa cca gct cga Pro Lys Asn Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg 65 70 75 80	399										
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Ile	Val	Ser	Thr	Thr	Phe	Leu 135	Val	His	Leu	Val	Val 140	Met	tca Ser	Asp	Leu	591
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110

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Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg  -10 -5 1  cgt cct tct atg gcc gct tca ggc act tct tgg ata tca tcg acc ctc Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu  5 10 15  gca cac tct ttg tca ctg aga gac gtc tca gag agg ctg tgc agc tgc Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys  20 25 30  tgg agg act ata agc atg gga ccc tgc ggc ggg tca cca atg aac Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn  35  40  36  37  38  39  40  30  Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr  50  55 60 65  55 60 65  56  65  65  65		60
Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg  -10 -5 1  cgt cct tct atg gcc gct tca ggc act tct tgg ata tca tcg acc ctc Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu  5 10 15  gca cac tct ttg tca ctg aga gac gtc tca gag agg ctg tgc agc tgc Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys  20 25 30  tgg agg act ata agc atg gga ccc tgc gcc cgg ggg tca cca atg aac Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn  35 40 45  agc tct gga gtg cac aga aaa tca agc agg cta ttc tac atc cgg aca Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr 50 55 60 65 cca atg aga aga tct tca tgc cat tta gaa tgt crg gtt ata ttc ctt Pro Met Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu  70 75 80  ttt gga cgc caa ttg taaktgttac cttcaaagga tttccttttc taaaaaatta 406 Leu Gly Arg Gln Leu  85  ttttaratgt ctaactttat gttattgctc acgggtattt gactgaattg ttgatttagg 466 ataagtcaat tcctggaggg aaattaccaa ataaaatgat atgtatttct taccacaaaa	cctcgagcg atg cac ctc ctt tcc aac tgg gca aac ccc gct tcc agc aga	111
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Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu  5 10 15  gca cac tct ttg tca ctg aga gac gtc tca gag agg ctg tgc agc tgc 207  Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys  20 25 30  tgg agg act ata agc atg gga ccc tgc gcc cgg ggg tca cca atg aac 255  Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn  35 40 45  agc tct gga gtg cac aga aaa tca agc agg cta ttc tac atc cgg aca 303  Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr  50 55 60 65  cca atg aga aga tct tca tgc cat tta gaa tgt crg gtt ata ttc ctt 351  Pro Met Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu  70 75 80  ttg gga cgc caa ttg taaktgttac cttcaaagga tttccttttc taaaaaatta 406  Leu Gly Arg Gln Leu  85  ttttaratgt ctaactttat gttattgctc acgggtattt gactgaattg ttgatttagg 466  ataagtcaat tcctggaggg aaattaccaa ataaaatgat atgtatttct taccacaaaa	-10	159
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Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr  50 55 60 65  cca atg aga aga tct tca tgc cat tta gaa tgt crg gtt ata ttc ctt 351  Pro Met Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu  70 75 80  ttg gga cgc caa ttg taaktgttac cttcaaagga tttccttttc taaaaaatta 406  Leu Gly Arg Gln Leu  85  ttttaratgt ctaactttat gttattgctc acgggtattt gactgaattg ttgatttagg 466  ataagtcaat tcctggaggg aaattaccaa ataaaatgat atgtatttct taccacaaaa 526		303
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cccgtttgag ctcggtatcc tagtgcacac gccttgcaag cgacggcgcc atg agt
                                                        Met Ser
                                                                      164
ctg act tcc agt tcc agc gta cga gtt gaa tgg atc gca gca gtt acc
Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala Val Thr
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                                 -15
att gct gct ggg aca gct gca att ggt tat cta gct tac aaa aga ttt
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Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys Arg Phe
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tat gtt aaa gat cat cga aat aaa gct atg ata aac ctt cac atc cag
Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His Ile Gln
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aaa gac aac ccc aag ata gta cat gct ttt gac atg gag gat ttg gga
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Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp Leu Gly
                                    35
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                                                                      356
gat aaa get gtg tac tgc egt tgt tgg agg tee aaa aag tte eea tte
Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe Pro Phe
                                50
                                                                      404
tgt gat ggg gct cac aca aaa cat aac gaa gag act gga gac aat gtg
Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp Asn Val
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                                                                      454
ggc cct ctg atc atc aag aaa aaa gaa act taaatggaca cttttgatgc
Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
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                                                                      514
tgcaaatcag cttgtcgtga agttacctga ttgtttaatt araatgacta ccacctctgt
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51

99

147

195

243

291

342

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aac atg ttg aag aaa tat tot cat cac cgg aat att got aca tac tat	156
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Gly Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp	
-25 -20 -15	
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Leu Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys	
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10 15 20	240
msg gaa atc tta cgg ggg ctg art cac ctg cac cag cat aaa gtg att	348
Xaa Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile	
25 30 35	306
cat cga rat att aaa ggg caa aat gtc ttg ctg act gaa aat gca gaa	396
His Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu	
40 45 50	444
gtt aaa cta gtg gac ttt gga rtc akt gct cag ctt gat cga aca gtg	444
Val Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val	
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ggc agg arg aat act ttc att gga act ccc tac tgg atg gca cca raa	7.74
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105 110 115	
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Pro Leu Ser Val Thr Cys Thr Pro	
120 125	
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gcttggtaaa aaatcacagc cagcgaccag caacagaaca attgatgaag catccattta	
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										ME	et Pr	ie De	eu II		la beu	
														cac His		104
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														tac Tyr		200
acc Thr	cgg Arg	gag Glu	cag Gln	gag Glu 45	cgc Arg	ggc Gly	cac His	gcc Ala	gcg Ala 50	ttg Leu	cgc Arg	agg Arg	agg Arg	gag Glu 55	gcc Ala	248
														cat His		296
														atg Met		344
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														aat Asn		440
		acc Thr	_			taaa	aacaa	aac a	aaaca	atgag	gt ag	gtct	gcata	a		488
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		tct g								caca	gat	gata	ttt 1	tgaaq	ggaaag	608 644
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aag gca aa Lys Ala A					tgagggag	aa ctc	agataa	a		336
aatattttca attttgtata aaacaaaaa	a tacgti a ctatta	atgtt tt	ttttctt gaaagtc	g tga	ttttat agagtaa	aaatat gggata	ttaa g ttaa a	atat tgta	tttat tccgt	396 456 472
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	Ser											tct		agt Ser		591
Arg					Ser	ctc				Gln	cac			ggc Gly		639
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		Thr					Leu					Leu		ccg Pro		783
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Arg		_	ggc Gly		Cys		taai	ttcca	agc a	actt	275 :ggg:	ag go	ccaa	ggcag	3	1122
cta ctc aga tat	caaaa agaaa ttgta ttaa	aag a gga t gcc a tat a	aaata tgagg actgo atata	aaaa gtggg cacto ataa	at as ga gg cc ag aa co	atago gato gooto cagao	etgg ettg gggt getg	g tgi g agg g aca a caa	ggt gctg agcg atga	ggca ggag agac cact	gcag cctg	gcate gaggt gtcte gaace	gta q ttg q caa q att q	gtcco cagto aatat gcata	tgtct agcta gagctg gtata accttc	1242 1302 1362 1422
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Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val

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gct cag gtg aga ggt gat agc tat gaa agc ggc tgt tta gga aga aca	350
Ala Gln Val Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr	
35 40 45	398
ggt gct cga gtt tgg ctt ttc att ggt ttc atg ttg atg ttt ggg tca Gly Ala Arg Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser	376
50 55 60 65	
ctt att gct tcc atg tgg att ctt ttt ggt gca tat gtt acc caa aat	446
Leu Ile Ala Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn	
70 75 80	
act gat gtt tat ccg gga cta gct gtg ttt ttt caa aat gca ctt ata	494
Thr Asp Val Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile	
85 90 95	542
ttt ttt agc act ctg atc tac aaa ttt gga aga acc gaa gag cta tgg Phe Phe Ser Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp	542
100 105 110	
acc tgagatcact tottaagtca cattttcctt ttgttatatt ctgtttgtag	595
Thr	
ataggttttt tatctctcag tacacattgc caaatggagt agattgtaca ttaaatgtt	
tgtttcttta catttttatg ttctgagttt tgaaatagtt ttatgaaatt tctttattt	
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ctg cgc ttc ctg agg gct gac ggc gac ctg acg cta cta tgg gcc gag Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu Thr Leu Leu Trp Ala Glu -5 10	149
tgg cag gga cga cgc cca gaa tgg gag ctg act gat atg gtg gtg tgg Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu Thr Asp Met Val Val Trp 15 20 25	197
gtg act gga gcc tcg agt gga att ggt gag gag ctg gct tac cag ttg Val Thr Gly Ala Ser Ser Gly Ile Gly Glu Glu Leu Ala Tyr Gln Leu 30 35 40	245
tct aaa cta gga gtt tct ctt gtg ctg tca gcc aga aga gtg cat gag Ser Lys Leu Gly Val Ser Leu Val Leu Ser Ala Arg Arg Val His Glu 45 50 55	293
ctg gaa agg gtg aaa aga aga tgc cta gag aat ggc aat tta aaa gaa Leu Glu Arg Val Lys Arg Arg Cys Leu Glu Asn Gly Asn Leu Lys Glu 60 65 70	341
aaa gat ata ctt gtt ttg ccc ctt gac ctg acc gac act ggt tcc cat Lys Asp Ile Leu Val Leu Pro Leu Asp Leu Thr Asp Thr Gly Ser His 75 80 85 90	389
gaa agc ggc tac caa agc tgt tct cca gga att tgg tagaatcgac Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly Ile Trp 95	435
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tggtagaatc gacattctgg tcaacaatgg tgga atg tcc cag cgt tct ctg tgc	175
Met Ser Gln Arg Ser Leu Cys	
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atg gat acc agc ttg gat gtc tac aga rag cta ata gag ctt aac tac	223
Met Asp Thr Ser Leu Asp Val Tyr Arg Xaa Leu Ile Glu Leu Asn Tyr -55 -40 -45	
-55 -50 -45 -45 tta ggg acg gtg tcc ttg aca aaa tgt gtt ctg cct cac atg atc gag	271
Leu Gly Thr Val Ser Leu Thr Lys Cys Val Leu Pro His Met Ile Glu	
-35 -30 -25	
agg aag caa gga aag att gtt act gtg aat agc atc ctg ggt atc ata	319
Arg Lys Gln Gly Lys Ile Val Thr Val Asn Ser Ile Leu Gly Ile Ile	
-20 -15 -10	
tot gta cot ott too att gga tao tgt got ago aag cat got oto ogg	367
Ser Val Pro Leu Ser Ile Gly Tyr Cys Ala Ser Lys His Ala Leu Arg	
-5 1 5	
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Gly Phe Phe Asn Gly Leu Arg Thr Glu Leu Ala Thr Tyr Pro Gly Ile	
10 15 20 25	
ata gtt tct aac att tgc cca gga cct gtg caa tca aat att gtg gaa	463
Ile Val Ser Asn Ile Cys Pro Gly Pro Val Gln Ser Asn Ile Val Glu	
30 35 40	
aat too ota got gga gaa gto aca aaa act ata ggo aat aat gga aac	511
Asn Ser Leu Ala Gly Glu Val Thr Lys Thr Ile Gly Asn Asn Gly Asn	
45 50 55	559
cag tee cae aag atg aca ace agt egt tgt gtg egg etg atg tta ate	555
Gln Ser His Lys Met Thr Thr Ser Arg Cys Val Arg Leu Met Leu Ile 60 65 70	
60 65 70 agc atg gcc aat gat ttg aaa gaa gtt tgg atc tca gaa caa cct ttc	607
Ser Met Ala Asn Asp Leu Lys Glu Val Trp Ile Ser Glu Gln Pro Phe	•••
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Leu Leu Val Thr Tyr Leu Trp Gln Tyr Met Pro Thr Trp Ala Trp Trp	
90 95 100 105	
ata acc aac aag atg ggg aag aaa agg att gag aac ttt aag agt ggt	703
Ile Thr Asn Lys Met Gly Lys Lys Arg Ile Glu Asn Phe Lys Ser Gly	
110 115 120	
gtg gat gcm rac tot tot tat ttt aaa ato ttt aag aca aaa cat gac	751
Val Asp Ala Xaa Ser Ser Tyr Phe Lys Ile Phe Lys Thr Lys His Asp	
125 130 135	
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<222> 46..585

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80

95

175

120 115 Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn 130 135 His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu 150 145 Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His 160 165 Thr Ala Ala Leu Pro Ala

Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100

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-50 -45 Ser Gly Leu Ser Glu Val Val Glu Ala Ser Ser Leu Ser Trp Ser Thr -35 -30 Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser -15 -20 Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr 20 15 Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro 35 30 Thr Arg Leu Ile Ala Thr Ile Met Val Leu Leu Cys Phe Ala Leu Thr 50 4.5 Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe 65 70 Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile 85 80 Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala 100 95

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45 50 55 Leu Ala Hiş Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala

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80

Pro Gly Cys Tyr Arg Tyr

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               -80
Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
                                                   -55
                               -60
           -65
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
                                               -40
                           -45
       -50
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
                                           -25
                      -30
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
                                       -10
                   -15
Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile
               1
Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val
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Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro
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Gly Tyr Leu Met Gly
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<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 393

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Thr Asn Thr Leu Thr Asp Met Gly Ser Phe Asp Arg Glu Ser 5 10 -15

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Ser

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<220>
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<400> 395

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 Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro -20
 -15
 -10

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 5

 Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 10
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 Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 25
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 Trp Gly Gln Gly Thr His Ser Ser Leu

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Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe -70 -65 -60 Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu -50 -45 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Gln Lys -25 -35 -30 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -15 -20 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala -5 1 Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 10 15 20 Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 30 35 Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 50 45 His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 60 65 Phe Ser Met Val Gly

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WO 99/31236

<220> <221> SIGNAL <222> -20..-1

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Val Pro Arg Cys Phe Glu Xaa Cys Val 50

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Pro Xaa Lys Leu Arg Gln 65

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 -20
 -15

 Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser -10
 -5
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 Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro 5
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 Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg 25
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120 125 130

Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln
135 140 145

Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe

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Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr
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Arg Ser Ile

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-25 - -20 - -15

Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro
-10 -5 - 1 5

Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu Leu
10 15 - 20

Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu
25 - 30 - 35

Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His
40 45 - 50

Ala His Trp Xaa Ser Xaa

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Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met 45 50 55 Val Arg

Val Arg

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1

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Asn Pro Phe Leu Trp Lys Leu

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Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser

25

Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser

<210> 414 <211> 170 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -79..-1 <400> 414 Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro -75 -70 Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly -60 -55 Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe -40 -45、 Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln -25 -20 Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe -10 -5 Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa 15 10 Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe 30 25 Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa 40 45 Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala 60 55 Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln 70 75 His Tyr Ile Arg His Ala Arg Gly Gly Leu . 90 85

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His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr Pro Arg Ser Gly Thr
5
10
15
20
Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln Asn Thr Pro Lys Ile
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Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu Glu Lys Ser Ile Met
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Leu

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Met Ile Xaa Leu Arc

Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp -25 -20 -30 Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln -15 -10 Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val 10 Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu 20 25 Val Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser 40 45 Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe 60 Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 75 Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 90 Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser 100 105

Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 120 125 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 135 140 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 150 155 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 165 170 . 175 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 180 185 190 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 195 200 205 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 215 220 Leu Phe Phe Tyr Asp Gln His Gly Gly Glu Val Ile Gly Val Leu Trp 230 235 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 245 250 Gly Arg Met Val Met Ser Arg Gly Gly Glu Leu Val Met Val Pro Asn 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 280 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 295

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5 10 15
Glu Glu Gln Lys Xaa Ser Gly Ile Met
20 25

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Arg Cys Ser Gly Ser Pro Leu Pro Leu 5

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<221> SIGNAL <222> -65..-1

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<400> 430

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                                    -60
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
           -50
                               -45
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
                           -30
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
    -20
                       -15
                                           -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Phe Ile
           15
                               20
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
                           35
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
                       50
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                   65
                                       70 .
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
              80
                                  85
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
           95
                               100
                                                105
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
        110
                           115
                                               120
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
                       130
                                           135
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
140
                   145
                                       150
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
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               160
Gly Tyr Glu Glu Leu Leu Thr Ser
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-35

Ile Gly Tyr Arg Asn Leu Gly Phe Thr Ser Met Cys Ile Leu Phe His
-20

-15

Cys Leu Leu Ser Phe Gln Val Phe Lys Lys Lys Arg Lys Leu Xaa Leu

Phe

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Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp

Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu

Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser

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<210> 436

<211> 162 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 436 Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala -15 -10 Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln 10 Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser 20 25 Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys 40 Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro 55 Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly 70 75 Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu 90 Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln 105 Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu 120 125 Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln 130 135 Glu Gly 145

<210> 437 <211> 110 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1 <400> 437 Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu -15 -10 Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile 1 Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu 20 Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly 40 35 Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro 50 55 . Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln 70 Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser 80 85 <210> 438

<211> 71 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 438 Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val -10 1 -5 Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile 10 Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys 25 30 Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln Val Pro Arg Arg Ala Gly 50

<210> 439
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 439

Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
-20 -15 -10

Ser Leu Asn Thr Leu Leu Leu Gly Gly Val Asn Lys Ile Ala Glu Lys
-5
Ile Cys Gly Asp Leu Lys Asp Pro Cys Lys Leu Asp Met Asn Phe Gly
10
Ser Cys Tyr Glu Val His Phe Arg Tyr Phe Tyr Asn Arg Thr Ser Lys
20
Arg Cys Glu Thr Phe Val Phe Ser Ser Cys Asn Gly Asn Leu Asn Asn
45
Phe Lys Leu Lys Ile Glu Arg Glu Val Xaa Cys Val Ala Lys Tyr Lys
60
Fro Pro Arg
75

<210> 440 <211> 169 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

<400> 440 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu -20 -15 Leu Leu Pro Leu Ala Pro Ala Ala Gln Asp Ser Thr Gln Ala Ser -5 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala 10 15 20 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala 30 35 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu 45 50 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr 60 65 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser 80 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser 95 Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val 110 115 Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp 125 130 Arg Thr Pro Asp Leu Pro Ala Leu Ala

Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 -50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -30 -35 -40 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -20 -25 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro -10 -5 Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 10 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser Tyr Ser Thr Lys Arg Ser Pro

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 442 Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg -10 -5 Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg 10 Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Xaa Arg Thr Lys Tyr Glu 25 Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp

-25

10

-10 Ala Thr Arg Ile Pro Leu Asn Gly Thr Trp Leu Phe Thr Pro Val Ser

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1 <400> 443 Met Ser Trp Thr Val Pro Val Val Arg Ala Ser Gln Arg Val Ser Ser -30 Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu Cys Pro Arg Gln

-15

Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val 40 Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu 55 Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met 70 Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys 85 90 Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr 105 100 Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln 120 115 Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr 135 Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu 150 155 Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile 165 170 Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly 185 180 Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly 195 200 Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala 215 Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp 230 235 Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr 250 245 Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser 265 260 Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His 275 280 285 Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val 290 295 Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu 310 315 Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser 325 330 Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu 340

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<210> 444
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
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<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                               -25
    -35
                   -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                                         -10
                      -15
-20
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
-5
                  1
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
 -25
                      -20
                                         -15
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
                  -5
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
                             15
Thr Arg Gly
      25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
                -25
                                      -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
               -10
                                   - 5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                           10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                       25
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 60 55 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn 75 Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln 90 95 Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu 105 110 Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His 120 125 Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg 140 135 Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu 150 155 Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr 170 175 165、 His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser Ser His Ser Arg 190 185 Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg 195 . 200 205 Gln Leu

<210> 448 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 448

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -55 -50 Arg Gln Arg Arg Gln Lys Leu Leu Ala Gln Leu His His Arg Lys -35 -30 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -25 -20 -15 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 **-5** Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu 25 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

Pro Glu Phe His Ile Glu Ile Leu Ser Ile

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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
               -55 -50
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
-45
                 -40
                                 -35
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
                                                  -15
              -25
                                -20
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
          -10
                   -5
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
                  10
His Pro Cys Ala Thr Tyr Pro Pro Xaa
        25
<210> 450
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 450
Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe Thr
               -20
                                       -15
Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro
               - 5
                                  1
Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile
         10
                           15
                                    20
Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly
              30
                                        35
Phe Asp Leu Asp Met Asp His Thr Ile
  40
                     45
<210> 451
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -34..-1
<400> 451
Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser
              -30
                               -25
```

Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser

Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys

-10

10

-5

-15

20

Ala Ile Ile Leu Met Lys

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<210> 452
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
           -35
                               -30
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
                           -15
                                               -10
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
              15
                                   20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
           30
                              35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
                           50
                                             55
Ala Ile Gly Xaa His Leu Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
                      65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
                  80
<210> 453
<211> 166
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
    -35 -30 -25
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                       -15
                                           -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
                   1
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
                              20
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
                           35
                                             40
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
                       50
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
                   65
                                       70
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                                  85
Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg
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100 Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu

120

115

95

Ser Ser Lys Lys Val His 125

<210> 454 <211> 180 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -25 、 -20 -15 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg 1 - 5 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 10 15 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 30 35 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 50 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 65 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 75 80 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 110 115 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 130 Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg 140 145 Arg Asn Trp Glu

<210> 455 <211> 91 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -64..-1

<400> 455 Met Thr Pro Arg Ile Leu Ser Glu Val Gln Phe Ser Ala Phe Cys Pro -55 -60 Tyr Trp Thr Ile Ala Arg Ile Leu Glu Arg Val Gly Ser Ala Cys Phe -45 -40 -35 Arg Leu Glu Leu Cys Ala Ala Ile Val Gly Tyr Phe Val Leu Asp Val -25 -20 -30 Arg Thr Phe Leu Phe Ile Val Val Cys Val Ile Cys Val Thr Leu Asn -10 -5 Phe Pro Arg Phe Tyr Phe Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly 10 Thr Pro Pro Ile Gly Val His Ile Pro Ser Pro

20 25

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa
           -20
                        -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
 - 5
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                   15
                                      20
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
               30
                                  35
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                               50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                           65
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                       80
                                           85
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                   95
                                       100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
                                   115
               110
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
           125
                               130
                                                   135
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                           145
                                               150
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                       160
                                           165
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
                   175
                                      180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Xaa Leu Pro
                                   195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
                               210
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
                           225
Xaa
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<210> 457
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
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Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -30 -40 -35 Leu Leu Cly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -15 -20 -25 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -5 -10 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 15 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 80 Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 95 90 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 105 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp Glu

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<210> 458
<211> 107
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
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<400> 458

70

Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg
-25 -20 -15

Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser
-10 -5 1

Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile

5 10 15 20

Arg Ala Val Ser Hig Thr Arg Val Thr Luc Luc Arg Leu Luc Val Cyc

Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys
25
30
35
Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val

40 45 50

Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu

55 60 65 Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly

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<210> 459
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
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<400> 459 Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr -10 -5 Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr 10 15 Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys 25 30 Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg 60 Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg 75 Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln 90 Phe Leu Ile Pro Asn Leu Ala Leu Asn 100 105

<210> 461 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 461 Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -5 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 10 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 30 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn 40 45 Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His 55 60 Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser 75

Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

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85 95

<211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 462 Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala -40 -35 -30 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -25 -20 -15 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu -5 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 10 15 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 35 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn 45 50 Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 65 Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr 75 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu 95

<210> 463 <211> 232 <212> PRT

<210> 462

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -30..-1

<400> 463

Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val -25 -20 Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa -10 -5 Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu 10 Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu 20 25 30 Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 40 45 Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser 60 Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly 75 Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 90 Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

105 110 100 Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val 120 125 Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys 135 140 Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val 155 160 Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp 170 175 Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu 185 Val Lys Cys Lys Phe Leu Tyr Asn 200

<210> 464 <211> 61 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 464

<210> 465
<211> 34
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -19..-1

<400> 465
Met Phe Leu Lys Ser Gly Ala
-15
Cys Trp Leu Glu Arg Lys Asp

Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu

-15

-10

-5

Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro

1

5

10

Gly Arg

15

<210> 466 <211> 215 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1

<400> 466

Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -50 -45 Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu -30 -25 -35 Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -20 -15 Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser 15 20 Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met 35 Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe 50 Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 65 Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 80 85 Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu 95 100 Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 115 Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr 130 135 Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile 145 Ile Ile Arg Lys Cys Phe Ile

<210> 467 <211> 27 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1

<400> 467 Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr Ser Lys Arg -10 Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe 1 5

<210> 468. <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1

<400> 468

Met Cys Ser His Ala Ser Met Ser Phe His Thr Leu Phe His Leu Leu -15 -20 Phe Leu Pro His Tyr Ile Glu Thr Phe Lys Pro Gln Ser Lys His Cys -5 1 Phe Phe Trp Ile Ala Ala Phe Leu Thr Ser Leu Leu Thr Pro Gln Ser 15 Leu Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe 35 30 Pro Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa 50 45 Tyr Trp Asp Asn Leu 60

. <210> 469 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 469 Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala -5 -10 -15 Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu 10 Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu 25

<210> 470 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -43..-1

Pro Asn Phe 35

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
            -10
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
                              10
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
   20
                       25
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
                    40
<210> 472
<211> 179
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL <222> -58..-1 <400> 472 Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His -50 -45 Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu -35 -30 Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile -20 -15 Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala -5 1 Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly 10 15 Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile 30 35 Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa 45 Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser 60 His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro 75 80 Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys 95 90 Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly 105 110 Gln Val Asn 120

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<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -71..-1
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<400> 473 Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg -65 Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile -50 -45 Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp -35 -30 Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu -20 -15 Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His 30 Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala 50 Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp 65 Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu 80 85 Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile 95 100 Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala 115 Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu 125 130 Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile 145 Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg 160

<210> 474 <211> 178 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1

<400> 474

Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe -30 -25 Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile -15 -10 Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu 20 Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn 50 Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 65 70 His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr 85 Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

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100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
                                    120
 110
                       115
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
  125
                                        135
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
 -20
                      -15
                                         -10
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
-5
                  1
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
         15
                           20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
                          35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
                     50
                                        55
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
                 65
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
                    -15
            -20
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
           - 5
                             1
Val Leu Gly Val Phe Phe Pro Ile Leu
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -27..-1

<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

225

<222> -18..-1

<400> 478 Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -15 -10 -5 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 35 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu 55 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 135 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 150 145 155 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 195 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

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<210> 479

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<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                       -15
                                           -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
                               20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                           35
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                       50
                                           55
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                                       70
                  65
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
               80
                                   85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
                               100
                                                   105
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
       110
                           115
Gly Lys Val Lys Ser Phe Lys
   125
                       130
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                                       -15
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
                       30
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
                                       50
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
Gln Ser Lys Lys Leu Glu Lys Lys Glu Thr Ile Thr Glu Ser Ala
                               80
Gly Arg Gln Gln Lys Lys Ile Glu Arg Xaa Xaa Xaa Xaa Leu Xaa
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Asn Asn Asn Arg Asp Leu Ser Met Val Arg Met Lys Ser Met Phe Ala 110 115 Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ile Phe 125 130 Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa 140 145 Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys 155 160 165 Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn 170 175 180 Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln 190 195 Ala Gly Gly Phe Leu Gly Pro Pro Pro Pro Ser Gly Lys Phe Ser 205

<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1

<400> 481

Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -90 -85 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 -65 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -50 -55 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -20 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 15

Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 55

Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 70

Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Asp Ala 85

Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro 105

Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa

Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser

30

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -39..-1

<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -35 -30 -25 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -20 -15 -10 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val 1 Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 10 15 20 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala 30 Arg Leu Leu Thr His Trp

45

<210> 483

<211> 40

<212> PRT

<213> Homo sapiens

<220'>

<221> SIGNAL

<222> -27..-1

<400> 483

Leu Ser Leu Arg Ser Ala Met Ser

10

<210> 484

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly
-15 - -10 - -5

Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met
1 5 - 10 - 15

Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys
20 - 25 - 30

Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala

35 40 45

Thr

<210> 485

<211> 130

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -55..-1 <400> 485 Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu -50 -45 Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg -25 -30 Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile -10 -15 Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr 1 Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val 20 10 15 Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa 35 30 Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg 45 50 Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp Ala Leu 75 <210> 486 <211> 209 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -84..-1 <400> 486 Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu -80 -75 Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr -65 -60 Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly -45

Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu -30 -25 Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu -15 -10 Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly 20 Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val 35 Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His 50 55 Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa 70 65 Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg 85 Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

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100
                                             105
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
 110
                      115
                                         120
His
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
    -15
                  -10
                                          -5
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                                     10
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
            -25 -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
           -10
                             -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
  5
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
       -50
                          -45
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
  -35
                      -30
                                         -25
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                  -15
                                     -10
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Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala

Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Val Pro Gly 25 20 Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu Asp Ser Trp 35 40 Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val Arg Arg 55 50 His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu Asp Pro 65 70 Asn Glu Cys Gly Tyr Gln Pro Pro Gly Ala Pro Pro Gly Leu Gly Ser 85 Met Pro Ser Ser Cys Gly Pro Arg Ser Xaa Lys Arg Ala Xaa Xaa 100 Thr Arg Ser 110

<210> 490 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1 <400> 490

<210> 491 <211> 218 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -50..-1

<400> 491 Met His His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys -45 -40 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala -30 -25 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly -15 -10 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser 10 Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser 20 25 Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln 35 40 Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

55 Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser 70 Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp 85 90 Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly 100 105 Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp 115 120 Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe 135 130 Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro 150 Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln 165

<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 492

Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -15 -10 -5 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 40 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 55 60 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 85 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 105 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly 135 140 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 150 155 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 165 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 180 185 Ser Val Tyr Leu Gly Arg Ile Val

<210> 493

<211> 134

<212> PRT

<213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 493 Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly -10 Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala 20 Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile 35 40 Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro 50 55 Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg 65 70 Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu 85 Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly 95 100 Asp Glu Val Lys Lys Glu <210> 494 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly -10 - 5 Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly 20 25 Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr 40 Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His 55 . His Arg Glu Gly Asp <210> 495 <211> 292 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -29..-1

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<400> 495
Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe
               -25
                                   -20
Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr
           -10
                               -5
Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr
                       10
Leu Leu Pro Tyr Leu Leu Cly Val Asn Leu Phe Phe Thr
                   25
                                      30
Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu
                                  45
               40
Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn
                               60
Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His
                           75
Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val
                       90
Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile
                  105
                                     110
Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser
                                  125
              120
Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu
           135
                              140
                                                 145
Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe
                           155
                                              160
Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu
                       170
                                          175
Gly Phe Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe
180
               . 185
                                      190
Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
             200
                                  205
Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro
                              220
Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg
                          235
Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg
                 . 250
                                          255
Lys Lys Gln Glu
260
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<210> 496
<211> 122
<212> PRT
<213> Homo sapiens
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<221> SIGNAL <222> -56..-1

Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu 25 30 35 40

Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly 45 50 55

Ala His Pro Lys Val Leu Lys Val Ala Leu 60 65

<210> 497 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 497 Met Leu Xaa Leu Ser Arg Ala Thr Lys Xaa Gly Arg Ala Arg Trp Leu -25 -20 Met Pro Val Ile Pro Ala Leu Gln Glu Ala Xaa Ala Gly Gly Ser Arg -5 Gly Gln Glu Phe Glu Thr Ser Leu Ala Asn Met Glu Thr Glu Ala Gly 10 Glu Leu Leu Lys Pro Arg Arg Arg Leu Gln

<210> 498 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

25

<400> 498

 Met
 His
 Leu
 Leu
 Ser
 Asn
 Trp
 Ala
 Asn
 Pro
 Ala
 Ser
 Ser
 Arg
 Arg
 Pro

 Ser
 Met
 Ala
 Ala
 Ser
 Gly
 Thr
 Ser
 Trp
 Ile
 Ser
 Ser
 Thr
 Leu
 Ala
 His
 His
 His
 His
 His
 His
 Arg
 Arg
 Arg
 Ile
 Ser
 Gr
 Trp
 Arg
 Arg
 Ile
 Trp
 Ile
 Ser
 Ser
 Cys
 Trp
 Arg
 Arg

<210> 499 <211> 99 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -13..-1
<400> 499
Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro
           -10
                                - 5
Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His
                                           15
                       10
Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg
                   25
Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser
                                   45
Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met
                               60
Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly
       70
                        75
Arg Gln Leu
   85
<210> 500
<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 500
Met Ser Leu Thr Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala
                                        -15
                    -20
Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys
               -5
                                   1
Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His
     . 10
                           15
                                               20
Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp
                       30
                                           35
Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe
                                       50
                   45
Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp
               60
                                   65
Asn Val Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
<210> 501
<211> 183
<212> PRT
<213> Homo sapiens
<220>
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<220>
<221> SIGNAL
<222> -15..-1

<400> 501
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15
-10
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu

10 Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu 40 Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn 55 60 Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys 75 70 Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg 90 Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala 105 Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val 120 125 Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu 135 140 Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly 150 155 Thr Gly Gln Asp Phe Lys Glu 165

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 Ala
 Trp
 Trp
 Trp
 Asp
 Ser
 Ser
 Glu
 Arg
 Met
 Lys
 Ser
 Arg
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 Arg
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 Arg
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Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn

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Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 35 40 45

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<220>

<221> SIGNAL

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Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg

Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys
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Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly 30 35 40

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Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu
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Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

Ser Asm Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg
10 20 25

Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp 65 Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe 85 80 Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser 95 100 Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys 115 120 110 Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro 130 Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn 150 145 Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly 165 155 160 Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp 180 175 Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala 190 195 Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe 205 210 His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala 225 230 220 Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu 240 245 Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu 255 260 Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu 270 Ser Gly Ser Cys Leu 285

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<221> SIGNAL

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 -15

 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile -10
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 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys 25
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                                      15
Thr Asp Met Val Val Trp Val Thr Gly Ala Ser Ser Gly Ile Gly Glu
Glu Leu Ala Tyr Gln Leu Ser Lys Leu Gly Val Ser Leu Val Leu Ser
        40
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Ala Arg Arg .Val His Glu Leu Glu Arg Val Lys Arg Arg Cys Leu Glu
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Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
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                           15
                                              20
Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
                       30
                                          35
Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
                   45
                                      50
Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
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Asn Asn Ala Leu Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg
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                               80
Gly Asp Asn Pro Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
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                                   .. 100
Phe Phe Asp Asp Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu
                       110
                                          115
Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
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Thr Lys Ser Tyr
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Arg Arg Pro Val Leu Leu Ala Gly Leu His Arg Gln Leu Leu Tyr
Ile Thr Ser Phe Val Phe Val Gly Tyr Tyr Leu Leu Lys Arg Gln Asp
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Tyr Met Tyr Ala Val Arg Asp His Asp Met Phe Ser Tyr Ile Lys Ser
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1080
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His Val Gly Asp Ser Ala Leu Met Gly Cys Val Phe Gln Ser Thr Glu
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